AS CARREIRAS DA CLOROQUINA E DA HIDROXICLOROQUINA COMO MEDICAMENTOS "MILAGROSOS" CONTRA A COVID-19: NARRATIVAS DA FRANÇA E DO BRASIL

LAS CARRERAS DE LA CLOROQUINA Y LA HIDROXICLOROQUINA COMO MEDICAMENTOS "MILAGROSOS" CONTRA EL COVID-19: RELATOS DE FRANCIA Y BRASIL

THE CAREERS OF CHLOROQUINE AND HYDROXYCHLOROQUINE AS "MIRACULOUS" ANTI-COVID-19 DRUGS: NARRATIVES FROM FRANCE AND BRAZIL

Luiz Villarinho Pereira MENDES[*]
Claudia Garcia Serpa OSORIO-DE-CASTRO[**]
Marilena CORREA[***]
Ilana LÖWY[****]

RESUMO: No início de janeiro de 2024, um artigo amplamente divulgado na revista *Biomedicine and Pharmacology* estimou que aproximadamente 17.000 pacientes com COVID-19 na França, Itália, Espanha, Turquia e EUA morreram

[*] Pos Doc position at Department of Medicines Policies and Pharmaceutical Services (NAF) of the Sergio Arouca National School of Public Health - Oswaldo Cruz Fondation (ENSP/Fiocruz), RJ, Brazil. Orcid: https://orcid.org/0000-0002-9027-0287. Contact: luizvillarinho@gmail.com.

[**] Senior researcher at Department of Medicines Policies and Pharmaceutical Services (NAF) of the Sergio Arouca National School of Public Health - Oswaldo Cruz Fondation (ENSP/Fiocruz), RJ, Brazil. Orcid: http://orcid.org/0000-0003-4875-7216. Contact: claudiaosorio.soc@gmail.com.

[***] Adjunct professor at the Institute of Social Medicine of the State University of Rio de Janeiro (IMS/UERJ), RJ, Brazil. Orcid: https://orcid.org/0000-0003-1742-8639. Contact: correamarilena@gmail.com.

[****] Senior researcher at Centre de recherche médecine, sciences, santé, santé mentale, Société (CERMES3) à l'Institut National de la Santé et de la Recherche Médicale (INSERM) Paris, France. Orcid: http://orcid.org/0000-0001-6963-0578. Contact: ilana.lowy@cnrs.fr.

como resultado do tratamento com hidroxicloroquina. A publicação deste artigo é um desfecho adequado para quase três anos de controvérsia sobre o possível uso de cloroquina e hidroxicloroquina para tratar a COVID-19. Reposicionados no início de 2020 como resposta milagrosa à pandemia de COVID-19, esses medicamenos tiveram um breve momento de celebridade mundial, apesar de dúvidas expressas por muitos especialistas quanto à sua eficácia e segurança. A carreira da hidroxicloroquina se encerraria na França em setembro de 2020, quando uma série de ensaios clínicos mostraram não apenas a ineficácia no tratamento da COVID-19, mas também reações adversas. No entanto, o uso da cloroquina e da hidroxicloroquina continuou no Brasil, onde o governo continuou a promovê-lo como a primeira opção terapêutica contra a COVID-19. Com base na metodologia desenvolvida pelos estudos sociais da ciência, nosso artigo reconstrói as trajetórias da hidroxicloroquina na França e no Brasil. O objetivo é elucidar as razões para a exceção brasileira, iluminando as consequências desastrosas do exercício de um poder político monolítico e de práticas antidemocráticas na regulação de medicamentos. Propõem-se novas reflexões sobre um tópico que tem sido visível na mídia e amplamente discutido na sociedade, mas que atraiu muito menos atenção na esfera acadêmica

PALAVRAS-CHAVE: Hidroxicloroquina. Estudos Sociais da Ciência. Controvérsias científicas. Trajetória de medicamentos. COVID-19.

RESUMEN: *En los primeros días de enero de 2024, un artículo ampliamente difundido en la revista Biomedicine and Pharmacology estimaba que aproximadamente 17.000 pacientes de COVID-19 en Francia, Italia, España, Turquía y EUA habían fallecido como consecuencia del tratamiento con hidroxicloroquina. La publicación de este artículo pone fin a casi tres años de controversia sobre el posible uso de cloroquina e hidroxicloroquina para tratar la COVID-19. Reposicionados a principios de 2020 como la respuesta milagrosa a la pandemia de COVID-19, estos fármacos disfrutaron de un breve momento de celebridad mundial, a pesar de las dudas expresadas por muchos expertos sobre su eficacia y seguridad. La carrera de la hidroxicloroquina llegaría a su fin en Francia en septiembre de 2020, cuando una serie de ensayos clínicos demostraron no sólo su ineficacia en el tratamiento de la COVID-19, sino también sus reacciones adversas. Sin embargo, el uso de cloroquina e hidroxicloroquina continuó en Brasil, donde el gobierno siguió promoviéndola como la primera opción terapéutica contra el COVID-19. A partir de la metodología desarrollada por los estudios sociales de la ciencia, nuestro artículo reconstruye las trayectorias de la hidroxicloroquina en Francia y Brasil. El objetivo es dilucidar las razones de la excepción brasileña,*

iluminando las desastrosas consecuencias del ejercicio de un poder político monolítico y de prácticas antidemocráticas en la regulación de medicamentos. Se proponen nuevas reflexiones sobre un tema que ha sido visible en los medios de comunicación y ampliamente debatido en la sociedad, pero que ha atraído mucha menos atención en el ámbito académico.

PALABRAS CLAVE: *Hidroxicloroquina. Estudios Sociales de la Ciencia. Controversias científicas. Trayectoria de los medicamentos. COVID-19.*

ABSTRACT: *In early January 2024, a widely publicized article in the journal Biomedicine and Pharmacology estimated that approximately 17,000 COVID-19 patients in France, Italy, Spain, Turkey, and the US died as a result of hydroxychloroquine treatment. The publication of this article is a fitting closure to nearly three years of controversy about the possible use of chloroquine and hydroxychloroquine to treat COVID-19. Repurposed in early 2020 as miracle answers to the COVID-19 pandemic, they had a brief moment of worldwide celebrity, despite the doubts expressed by many experts. Hydroxychloroquine's career ended in September 2020, when a series of clinical trials showed not only inefficacy to treat COVID-19 but also safety concerns. However, the use of chloroquine and hydroxychloroquine continued in Brazil, where the government continued to promote their use as the first therapeutic choice against COVID-19. Our study outlines the employ of these drugs in France and Brazil. Grounded in the methodology developed by social studies of science, our article reconstructs the trajectories of hydroxychloroquine in France and Brazil. It aims to elucidate the reasons for the Brazilian exception, illuminating the disastrous consequences of the exercise of a monolithic political power and of anti-democratic practices on drug regulation and proposes new reflections on a topic that has been visible in the media and widely discussed in society, but attracted much less attention in the academic sphere.*

KEYWORDS: *Hydroxychloroquine. Social Studies of Science. Scientific Controversies. Drug trajectory. COVID-19*

Introduction

Chloroquine (CLQ) and hydroxychloroquine (HCQ) are two 4-aminoquinoline drugs that were tentatively repurposed for use against SarsCov-2 in early 2020. Chloroquine is historically a drug of choice for *Plasmodium vivax* malaria. Hydroxychloroquine on the other hand is employed in autoimmune conditions

such as rheumatic disease and Lupus. The latter was promoted by a French infectious disease's expert, Prof. Didier Raoult, as an efficient cure for COVID-19. Some experts contested Raoult's claim, but the drug rapidly achieved worldwide attention.

The contentious debate about the efficacy of HCQ and CLQ in the treatment of COVID-19 ended, however, in September 2020, when a series of large-scale collaborative trials already displayed its lack of efficacy. Despite this, Brazilian public health policy persisted in adopting both drugs in the Brazilian health system as the first therapeutic choice against COVID-19 (ABRASCO, 2022). This view was enthusiastically endorsed by the then President of Brazil, Jair Bolsonaro, and by his Administration, which discredited the position of The Brazilian National Regulatory Agency (Anvisa). Notably, the Administration not only promoted use HCQ/CLQ as treatment but also as a "preventive" health intervention until late 2022.

Our text aims to explore why and how the Bolsonaro Administration successfully continued to impose its anti-scientific ideological position on COVID pandemics for over two years. This social phenomenon illustrates the intersections between politics and science in Brazil, a country ruled at that time by an extreme right-wing Government. Utilizing an approach grounded in social studies of science coupled with a political sciences perspective, we aim to understand the dynamics of the use of inefficient drugs during the COVID-19 pandemic in Brazil. This approach allows us to delve into the exercise of monolithic political power and anti-democratic practices, especially those related to sciences and medical practices, including drug regulation.

Our study is based on a broad review of the scientific and gray literature, media articles published in Brazil and around the world, and official Ministry of Health, Anvisa and Brazilian Senate documents. Almost three years after the beginning of the COVID-19 pandemic, we reconstructed the trajectories of HCQ/CLQ, offering new insights on a topic extensively discussed in society but less explored in the academic sphere.

Happy beginnings: Chloroquine and Hydroxychloroquine's meteoric rise

A mysterious outbreak of severe pneumonia was reported by Chinese authorities at the very end of December, 2019. WHO declared the new coronavirus Public Health Emergency of International Concern (PHEIC) on the 31 January, 2020; first lock-downs in Europe begun in late February and early March, and on the March 11, 2020, WHO declared the new disease - in the meantime named COVID-19 a pandemic (WHO, 2024).

Looking from a distance on the early developments of the hydroxychloroquine trajectory, one of the most striking elements is how fast the story of rise and fall of hydroxychloroquine unfolded. The first article on the - presumed- high efficiency of a well-known drug hydroxychloroquine, in preventing severe forms of COVID-19 was published on March 20, 2020. Although discussions on hydroxychloroquine continued in 2021 and 2022 in France with an epilogue in 2023, the main events took place during the first months of COVID-19's massive spread outside China.

The scientist behind the article that claimed that hydroxychloroquine prevented severe cases of COVID-19 was the French microbiologist Professor Didier Raoult, the director of Institut Hospitalo-Universitaire (IUC) Méditerranée Infection, an important medical-cum research center based in Marseille. Chinese physicians attempted in early February 2020 to apply chloroquine to treat COVID-19 patients. Raoult proposed to switch from chloroquine to its less toxic variant, hydroxychloroquine, and rapidly conducted a non-authorized clinical trial of the drug, which Raoult and his collaborators claimed had displayed remarkable efficacy.

An article detailing this non-randomized clinical trial of hydroxychloroquine underwent a fast-track review process, was accepted on March 19, 2020 and published online a day later. The publication of this article immediately generated significant interest among both professionals and the general public (GAUTRET *et al*., 2020). Raoult promptly gained national and worldwide fame, first through his highly popular French YouTube channel that disseminated information about the new drug. Subsequently, campaigns supporting hydroxychloroquine were launched simultaneously by French and US-based proponents. In France, a petition endorsing the administration of hydroxychloroquine for COVID-19 treatment, initiated by former Minister of Health Philippe Douste-Blazy, rapidly garnered tens of thousands of signatures. President Macron, likely influenced by the popularity of hydroxychloroquine, visited Raoult's laboratory in Marseille on 8 April, 2020.(PAYET, 2020; SCIAMA, 2020)

In the US, Georgy Rigano, a US lawyer and Fox News collaborator, uploaded a Google document praising the new therapy for COVID-19 on March 15, 2020, then secured the visibility of this innovation for Fox News. On March 16, Elon Musk tweeted a link to Raoult's paper to his nearly 33 million followers.(SAYARE, 2020; WONG, 2020). Fox News promotion of hydroxychloroquine led to an enthusiastic endorsement of this therapy by Presidents Trump and Bolsonaro (BAKER *et al*., 2020).

While the new treatment rapidly gained the support of prominent personalities, it received a much more critical evaluation from infectious disease experts. Several well-known French specialists strongly criticized the methodological choices made by the Marseille team, above all the lack of randomization, and of a properly constituted control group. On April 3, 2020 the International Society of

Antimicrobial Chemotherapy (ISAC), which had initially fast tracked the publication of Raoult's article in its house journal, went to the rather extraordinary length of publicly stating that "the article does not meet the Society's expected standard, especially relating to the lack of better explanations of the inclusion criteria and the triage of patients to ensure patient safety". ISAC blamed an unnamed 'Associate Editor' for a hasty and uncritical acceptance of Raoult's text (ISAC, 2020).

In Brazil, the proposal and public endorsement by the Bolsonaro Administration[1], of the off-label use of chloroquine and hydroxychloroquine prompted The Federal Council of Medicine (CFM), the professional board for physicians, to assert that the use of these drugs in COVID-19 could be based on a consensus between the prescriber and the patient (CFM, 2020).

Subsequently, the defense of "early treatment"[2] involving chloroquine/hydroxychloroquine and other drugs became a symbolic representation of the ongoing political battles in Brazil during the epidemic. An illustrative example occurred when Bolsonaro humorously remarked that "*Those on the right take chloroquine, those on the left take tubaína."* (Os que são da direita tomam cloroquina e os da esquerda tomam tubaína). This rhyme alludes to a very low-cost soft drink popular among the disenfranchised.[3]

Simultaneously the administration proposed the use of other drugs to be taken together for COVID-19 treatment and this came to be known as the "COVID kit".[4] This "kit" was not only advocated through official discourse but was also distributed in primary healthcare units in specific Brazilian municipalities aligned with the Bolsonaro government.

The proposal to repurpose hydroxychloroquine (HCQ) or chloroquine (CLQ) was particularly attractive to the Brazilian extreme right-wing government, characterized by a strong military presence. Notably, the main public laboratory supplying chloroquine during the COVID-19 pandemic was the Army's Chemical-Pharmaceutical Laboratory (LQFEx), sending a clear political message of the armed forces collaborating with Bolsonaro to safeguard the nation, facilitated by the drug's established production in Brazil for malaria treatment.

---

[1] Jair Bolsonaro began publicly defending chloroquine on March 21 on social media, two days after a press conference by President Donald Trump, in which Trump had declared that he had ordered the FDA - Federal Drug Administration - to speed up the approval of the use of chloroquine and hydroxychloroquine. The FDA did in fact approve the emergency use of chloroquine and hydroxychloroquine, but canceled it three months later after serious side effects were found (WRIGHT, 2021).

[2] Early treatment, according to its promoters, would be the use of HCQ/CLQ during the first days of COVID-19 infection. Health insurer Prevent Senior even coined the expression "Golden Day", i.e. the best day to start using the COVID-kit (BRASIL. SENADO FEDERAL, 2021).

[3] See: Poder 360. Quem é de direita toma cloroquina, quem é de esquerda, Tubaína, diz Bolsonaro. Vídeo, 19 de maio de 2020. Disponível em: https://www.youtube.com/watch?v=UrD5nNfVNDE.

[4] The "COVID-kit" consisted of a variety of combinations that invariably included chloroquine/hydroxychloroquine, azithromycin, ivermectin and other drugs, depending on the location. (BRASIL. SENADO FEDERAL, 2021).

As "early treatment" evolved into a asserted public policy, there was a deliberate effort to ramp up local chloroquine production. Between March and May 2020, LQFEx provided over 3.2 million 150mg chloroquine tablets to the Ministry of Health, concomitantly reducing the production of other essential medicines for the country.[5] Additionally, Brazil, aligning with the Trump administration, received a US donation of 3,016,000 tablets of hydroxychloroquine 200 mg from Sandoz Inc. (Novartis Group).

In essence, the Ministry of Health redirected the use of chloroquine, produced in public laboratories for the National Malaria Control Program[6], to treat COVID-19, leading to repercussions felt two years later when, in July 2022, the Ministry of Health admitted a shortage of chloroquine for malaria treatment (BANDEIRA, 2023). According to the Federal Pharmacy Council (CFF), the pharmacists' professional board, retail sales of hydroxychloroquine surged by 113.15% in 2020 compared to 2019 (BRASIL. SENADO FEDERAL, 2021). However, because of high demand, patients with autoimmune diseases could not buy their essential medicines.

The private pharmaceutical industry in Brazil played a significant role in the rapid surge of HCQ and CLQ by leveraging its influential propaganda machine. The Medicines Market Regulation Chamber (CMED) reported a 48% increase in the packaging of both chloroquine and hydroxychloroquine during the same period (BRASIL. SENADO FEDERAL, 2021).

One pharmaceutical manufacturer, Vitamedic experienced an astonishing 1458% increase in chloroquine sales. To achieve this, Vitamedic spent more than 700.000 BRL (142.000 USD) on advertisement in mass-circulation newspapers (BRASIL. SENADO FEDERAL, 2021). in blatant violation of the law that prohibits DTCA (direct-to-consumer-advertising) of prescription-only medicines (ANVISA, 2008).

Chloroquine, Hydroxychloroquine and randomized clinical trials

From April to June 2020, the status of hydroxychloroquine as an anti-COVID -19 drug remained undecided. There was initial indication that the risk-benefit ratio was possibly high but no firm proof had been forwarded as conclusive results from randomized clinical trials on hydroxychloroquine were not yet available.

[5] Despite being the exclusive producer, LQFEx reduced production by 1/3 of mycophenolate sodium 360 mg, a vital immunosuppressant drug for the 80,000 patients who had undergone a transplant in the country. The Brazilian Senate also investigated possible overbilling: the 2020 MoH drug purchase cost 167.21% more than that an equal purchase in 2019 (BRASIL. SENADO FEDERAL, 2021).

[6] The Farmanguinhos laboratory, linked to Fiocruz (Oswaldo Cruz Foundation), also produced and delivered more than 3 million chloroquine tablets (150mg) to the Ministry of Health. However, unlike LQFEX, it has always publicly stated that it produces chloroquine solely for the malaria program. (BRASIL. SENADO FEDERAL, 2021).

In April 2020, the US Food and Drug Administration (FDA) cautioned against the use of hydroxychloroquine or chloroquine for COVID-19 outside the hospital setting or clinical trials due to their potential risk for arrythmias (FDA, 2020). This warning stemmed from preliminary results of randomized clinical trials on hydroxychloroquine, indicating a lack of therapeutic efficacy and potential risks for specific patient groups, particularly elderly individuals with cardiovascular diseases. Raoult and his collaborators argued that chloroquine and hydroxychloroquine, aside from being cost-effective, were entirely safe, given their long-standing use by millions for malaria and autoimmune diseases. However, critics pointed out that patients in these groups had different profiles from those at the highest risk of COVID-19 complications elderly individuals and those with pre-existing chronic conditions. Moreover, COVID-19 affects the heart, greatly increasing the danger of using a drug known to induce heart arythmia. Accordingly, a key criticism of Raoult's work was the failure to include fragile patients with the highest risk in their experimental group, introducing a selection bias that, according to experts, could account for positive outcomes. Furthermore, critics argued that due to the high rate of spontaneous recovery from COVID-19, only large-scale randomized trials could provide scientific evidence of clinical efficacy (CASCELLA *et al*., 2023).

Brazilian experts were aware of early critique of chloroquine/hydroxychloroquine treatment. On May 15, 2020, Nelson Teich, resigned his position as Brazilian Minister of Health after a mere 29 days in office. One of the reasons cited for his resignation was a disagreement with President Bolsonaro regarding the widespread use of chloroquine for treating COVID-19 (PHILLIPS, 2020). Teich did not assert that this drug was ineffective; rather, he contended that there was insufficient evidence supporting its efficacy and particularly its safety.

Despite the FDA's warning, on May 18, 2020, Donald Trump, a fervent believer in the purported virtues of hydroxychloroquine, publicly declared that he had initiated a daily prophylactic regimen of the drug. This announcement drew criticism from medical experts and journalists (BENDIX, 2020).

On May 20, 2020, five days after Teich's resignation, the Brazilian Ministry of Health issued "Guidelines of the Ministry of Health on "early drug treatment" of patients diagnosed with COVID-19." (MS, 2020a). Subsequently, the National Health Council (CNS) (CNS, 2020), the social control body of the Unified Health System (SUS), and a group of scientists from Fiocruz (SUÁREZ-MUTIS; MARTÍNEZ-ESPINOSA; OSORIO-DE-CASTRO, 2020) took a stance against the Ministry of Health's directive. They asserted that there was no compelling scientific evidence to substantiate the use of chloroquine/hydroxychloroquine at any dosage or stage of COVID-19.

Unfortunately, in late May, the publication of the results from a large-scale study of hydroxychloroquine was marred by scandal. This multinational registry

analysis in The Lancet claimed that hydroxychloroquine did not reduce the risk of severe forms of COVID-19 (MEHRA *et al*., 2020). The data in this article were derived from the international database Surgisphere, comprising electronic health records from 169 hospitals on three continents. Observant readers of The Lancet, however, noted discrepancies, suggesting that some results from this database were fabricated. The owners of Surgisphere were unable to verify its reliability, leading to the withdrawal of The Lancet article (BOSELEY; DAVEY, 2020; DAVEY, 2020). Raoult viewed this incident as vindication of his position on the "tyranny" of leading medical journals and a decisive demonstration of the fallacy of arguments questioning the validity of his hydroxychloroquine studies based on methodological flaws. He gleefully stated that while The Lancet article had an impeccable methodology, it unfortunately relied on fraudulent data.

The Surgisphere episode was, albeit, interpreted as a call for greater vigilance of professional journals and reviewers, also as a sign that the self-surveillance mechanisms of the scientific community were efficient: a suspected article was denounced and rapidly withdrawn. In the following months, several other articles arrived at the same conclusion that the retracted Lancet publication did: clinical trials had shown that hydroxychloroquine had no positive effect on COVID -19 patients.(BOULWARE *et al*., 2020; FIOLET *et al*., 2021; SKIPPER et al., 2020). These results were confirmed later by large scale WHO clinical trial of COVID-19 therapies (WHO SOLIDARITY TRIAL CONSORTIUM, 2020).

WHO discontinued its clinical trials of hydroxychloroquine in July 2020, because the intermediary analysis did not display any therapeutic effects of the drug (REUTERS, 2020). From September 2020 on, there was an agreement among the experts worldwide that hydroxychloroquine was not an effective treatment of COVID-19. In 2020, robust studies already contraindicated its use (CAVALCANTI *et al.*, 2020; RECOVERY COLLABORATIVE GROUP *et al.*, 2020). Since March 2021, the WHO has not recommended the use of hydroxychloroquine for the prevention or treatment of COVID-19. At the beginning of 2023, the WHO cited 12 randomized clinical studies (n=8379) ratifying this contrary position (WHO, 2023). Accordingly, this substance was officially eliminated from the WHO's guidelines on drugs to prevent COVID-19 (LAMONTAGNE *et al.*, 2021), An editorial of the Journal of the American Medical Association (JAMA) from November 2020, summarized the experts' consensus on this topic: "The clear, unambiguous, and compelling lesson from the hydroxychloroquine story for the medical community and the public is that science and politics do not mix."(SAAG, 2020, p. 2161-2162)[7]

[7] For a sociological analysis of randomized clinical trials of hydroxychloroquine see Cosima Rughinis, Lorena Dima, and Sorina Vasile (2020).

Even though most Brazilian experts were in line with international recommendations (FALAVIGNA *et al*., 2020), the Federal Council of Medicine maintained its position and did not condemn the prescribing HCQ or CLQ drugs for COVID-19. As late as September 21, 2021, thus nearly a year after the establishment of a consensus on the ineffectiveness of CLQ/HCQ, Bolsonaro continued to defend "early treatment" of COVID-19 in his speech at the opening of the United Nations assembly.[8]

An unhappy end: how 4-aminoquinolines faded from sight.

The results of randomized clinical trials published between June and September 2020 marked the decline in the perceived effectiveness of hydroxychloroquine as a therapy for COVID-19. Another contributing factor to the abandonment of this drug was its diminishing role as a "last resort" treatment in the absence of other therapeutic alternatives. One of the earliest treatments for COVID-19 validated through randomized clinical trials was the corticosteroid dexamethasone; this treatment remained widely used during the COVID-19 pandemics. From July 2020 to 2021 a series of antiretrovirals (i.e. Remdesivir, Molnupiravir, Nirmatrelvir + Ritonavir) and biologics (i.e. Tocilizumab) were introduced as IV or oral drugs for preventing severe complications from COVID-19. Even if, eventually discarded as effective treatment, these drugs underwent clinical trials and eliminated the necessity for the use of remedies of questionable efficacy.

Controversies typically faded away gradually rather than abruptly. While public hospitals in Europe and North America abandoned the use of hydroxychloroquine as a COVID-19 therapy, some doctors continued to prescribe it, and certain patients persisted in believing in its efficacy (SCHULTZ *et al*., 2022). Furthermore, in France, hydroxychloroquine continued to be employed at Raoult's stronghold, IHU Mediterrannée Infection. Raoult remained highly popular in Marseille, partly due to his influence in local politics. His status as a "local hero" was solidified by the marketing of a "santon" (a figure used in nativity crèches) in his image and votive candles bearing his photograph, although the true sentiment behind these objects – whether genuine admiration, ironic expression, or a combination of both – remains unclear. In 2021, Raoult gained popularity among French opponents of mandatory COVID-19 vaccination, as he claimed that early treatment with hydroxychloroquine rendered COVID-19 a non-dangerous disease, thereby asserting the unnecessary nature of compulsory vaccination for the entire population. This further elevated

[8] Speech by the President of the Republic, Jair Bolsonaro, at the opening of the 76th UN General Assembly. Available at: https://www.gov.br/planalto/pt-br/acompanhe-o-planalto/noticias/2021/09/discurso-do-presidente-da-republica-jair-bolsonaro-na-abertura-da-76deg-assembleia-geral-da-onu.

Raoult's standing among fringe segments of the French population while intensifying animosity from mainstream French medical experts.

In 2022, Raoult reached the mandatory retirement age, and his attempts to extend his directorship of IHU Mediterrannée Infection were unsuccessful. Facing accusations of irregular conduct in clinical trials during the COVID pandemic he also encountered legal challenges.(AFP, 2021). A report from an official inspection mission that scrutinized the activities of his institution, published in July 2022, highlighted numerous questionable clinical practices. These concerns extended beyond the context of the COVID-19 pandemic, which Raoult and his collaborators argued justified the relaxation of some strict rules of clinical experimentation due to the emergency situation. The report also revealed an authoritarian and "tyrannical" management style by Raoult within the IHU (COQ-CHODORGE; PASCARIELLO, 2022). Responding to this report, the French government, in September 2022, decided to initiate legal proceedings against Raoult (AFP, 2022). However, there appeared to be no sense of urgency in the government's actions, and by May 2023, nearly all prominent French scientific and medical societies had signed a collective appeal urging the government to expedite the judicial examination of illegal clinical practices at IHU Mediterrannée Infection (COLLECTIF CALL, 2023).

If Didier Raoult's work was eventually rejected in France and in most parts of the world by 2020, in Brazil it was read with great enthusiasm by groups of doctors who supported the government in its policy of promoting early treatment, which guaranteed a much longer career for CLQ and HCQ: at least until December 2022.

In June 2020, when Brazil was on the verge of reaching a death toll of 50.000, the MoH introduced a protocol for the "early treatment" of children, adolescents, and pregnant women (MS, 2020b). As the country approached the somber milestone of 100.000 deaths in August 2020, the MoH's website encouraged patients with any symptoms to seek early treatment (FLOSS *et al*., 2022). In August 24, 2020, a group of doctors presented a letter advocating for "early treatment" as a means of improving the chances of curing the disease and preventing deaths. The MoH's website clarified that these doctors belonged to the 10.000-strong nationwide group known as the "Brazil Beating COVID-19 Movement"(MS, 2020c). In December 2020, when the prospect of purchasing anti-COVID vaccines had already arisen (SENADO FEDERAL, 2021), the Federal Government decided to invest 250 million BRL (50,85 million USD) in the acquisition of the COVID Kit, to be distributed through the Popular Pharmacy program (SANTOS-PINTO; MIRANDA; OSORIO-DE-CASTRO, 2021) and private drugstores (VARGAS, 2020).

The perspectives disseminated by the government became deeply entrenched in the Brazilian lay imagination, and their influence persisted until late 2022. In late 2021, following the emergence of the Omicron variant in Brazil, the demand for drugs included in the COVID kit, which had diminished in the first half of that year,

began to increase once more. Sales of hydroxychloroquine, for instance, witnessed an increase from 77.000 packages in April 2022 to nearly 92.000 in May of the same year (WIZIACK, 2022).

Questionable ethics surrounding the debate of non-evidence-based 4-aminoquinolines use during COVID-19

The Bolsonaro government justified its endorsement of hydroxychloroquine as the primary treatment for COVID-19 by invoking the principle of medical autonomy. Medicine, being an imprecise science, advocates of medical autonomy sustain, relies on the experiential knowledge of the physician, and clinical decisions represent the unique interaction between a healthcare professional and an ailing individual. Consequently, physicians possess the freedom to prescribe the treatment they deem most suitable for a particular patient. While the principle of medical autonomy, as applied to the prescription of hydroxychloroquine for COVID-19, might have been deemed acceptable in the initial stages of the pandemic, when the understanding of the drug's effects was only partial, its continued application, given the accumulating scientific evidence pointing to the lack of efficacy and potential harm of hydroxychloroquine, became increasingly detrimental as well as ethically and legally questionable.

In the early and tumultuous stages of the COVID-19 pandemic, the urgency to respond to the unfolding disaster occasionally led to risky clinical experiments and a disregard for the Hippocratic oath's principle "primum non nocere" (first do no harm). During this period, instances of potentially unethical conduct were observed even in prominent Brazilian public health institutions. A clinical trial conducted in Manaus (Amazonas, Brazil) in March and April 2020, investigated the use of chloroquine. In this trial potentially toxic doses (above the maximum daily dose of 600mg) were administered to trial participants (SUÁREZ-MUTIS; MARTÍNEZ-ESPINOSA; OSORIO-DE-CASTRO, 2020). Mortality rates were high in both, intervention and comparative groups, but somewhat higher in the group that received the higher doses of the drug (17% compared to 13.5%) (COLLUCCI, 2020). The trial was discontinued based on this result. Following the publication of the preliminary results, the researchers conducting the study faced accusations from some external observers of engaging in irresponsible experimentation on "human guinea pigs" and were held responsible for the deaths of 11 patients (NUNES, 2020).

Although the Manaus chloroquine trial was likely problematic, resulting in an unintended display of the drug's risks in early 2020, the organizers might have initially harbored hopes of discovering an efficient way to treat COVID-19. The situation markedly changed after the establishment of an international consensus

regarding the lack of therapeutic efficacy of hydroxychloroquine. In late 2020 the prescription of this molecule in the name of medical autonomy constituted, we argue, a clear breach of principles of medical ethics.

A Senate's Parliamentary Commission of Inquiry (PCI) on the COVID-19 pandemic was installed in April 2021 to investigate government actions and failures in fighting the epidemic, including ethical breaches and legal misadventures by health providers. One example is the scandal involving the health insurance company Prevent Senior. PCI indicted Prevent Senior for numerous irregularities. Testimonies from the company's employees revealed how Prevent Senior mandated the prescription of early treatment and the "COVID kit" throughout the pandemic. To preempt resistance to this measure, the company prioritized hiring professionals at the start of their careers, who were more likely to accept its rules (BRASIL. SENADO FEDERAL, 2021).

During the peak of the PCI debates, one of the main arguments employed by the company's management to justify their actions was the principle of medical autonomy. Using this argument, Prevent Senior attempted to absolve itself of responsibility by shifting all blame to its employees. This led to an intense legal battle. In addition to an indictment for a criminal partnership with the Federal Government to distribute ineffective drugs against COVID-19 to patients, Prevent Senior also faced charges for conducting a clinical study that was not approved by the National Ethics in Research Committee (CONEP). In this study, 636 patients received hydroxychloroquine and other ineffective drugs, resulting in nine deaths allegedly concealed by the company. Neither the patients nor their relatives had been informed that they were participating in a clinical trial, constituting unethical and illegal behavior.[9]

Witnesses in the PCI hearing also testified that even after the conclusion of the Prevent Senior infamous clinical study, "early prevention kits" continued to be distributed to more than 6.000 patients. The company's irregularities were compounded by the failure to advise healthcare staff on the use of personal protective equipment (PPE) and the issuance of false "disease identification" certificates to patients hospitalized after 14 days, artificially inflating the success statistics of the early treatment protocol (BRASIL. SENADO FEDERAL, 2021).

The saga of hydroxychloroquine continued, although in a much attenuated form, in France too. In late April 2023, Raoult and his colleagues made a last attempt to rehabilitate their approach by submitting a new paper, claiming that it demonstrated, through an analysis of files from over 30 thousand COVID-19 patients treated

[9] The principles of the participation of human subjects in the field of medical and biomedical research have already been established since the promulgation of the Declaration of Helsinki by the World Medical Association (1964), later harmonized at a global level by the publication of the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS) by WHO. Both are periodically revised and updated (WHO, 2011).

at IHU Mediterrannée Infection, that those who received hydroxychloroquine in the early stages of their illness rarely developed severe complications (MILLION *et al.*, 2023). However, severe critiques of this text mirrored the critiques of earlier publications by Raoult's group: the patients were pre-selected, and the study lacked an appropriate control group. In essence, it was seen as more of the same. This paper was consequently presented as additional evidence of the widespread use of unethical clinical practices at IHU Mediterrannée Infection (AUDUREAU, 2023). The authors ultimately decided to withdraw their submission, likely marking, at least in France, a final blow to a once celebrated "miracle therapy" (ROF, 2023).

While Didier Raoult experienced a spectacular fall from his meteoric rise as a proponent of hydroxychloroquine treatment, and is facing legal proceedings, the same fate did not befall Brazilian physicians who endorsed the unethical use of this drug. Numerous members of Bolsonaro's "parallel cabinet", who participated in ethically dubious clinical studies, continue to publicly defend the efficacy of "early treatment" of COVID-19 with hydroxychloroquine (PRAZERES, 2021). One of them was recently elected as a member for life of the Brazilian Academy of Sciences (BEZERRA, 2023).

There is little doubt that the hydroxychloroquine episode in Brazil harmed patients, but the extent of this harm remains a critical question. An important article by Pradelle *et al*., published in January 2024, argued that the use of hydroxychloroquine in the early stages of the COVID-19 pandemic in France, Italy, Spain, Turkey, and the US led to an estimated 17.000 deaths. In these countries, the systematic application of hydroxychloroquine to treat COVID-19 patients ceased in the fall of 2020. It could be particularly interesting to apply the methodology utilized by Pradelle *et al*. (2024) to estimate how many deaths can be attributed to the use of chloroquine/hydroxychloroquine in Brazil, given that Brazilian public policies, such as the distribution of the "early treatment" kit containing hydroxychloroquine, encouraged the massive use of this drug until December 2022 (PRADELLE *et al*., 2024).

Reflections on "users democracy" and the counterpoint of drug regulation

After facing severe criticism of the methodology in his clinical trials of hydroxychloroquine from leading French experts, Raoult launched a counterattack, including an opinion column in France's most influential newspaper, Le Monde. In this text, Raoult decried what he called "methodology maniacs", criticizing the bureaucratization of clinical research and asserting the forgetting of the physician's primary duty: saving lives. According to Raoult, the emotionally detached "meth-

odologists", often serving the interests of the pharmaceutical industry, stand in stark contrast to "real doctors" who are clinically oriented medical humanists (RAOULT, 2020). The argument that clinical experience overrides evidence from clinical trials was advanced in Brazil by the group *Médicos Pela Vida* (MPV), linked with Bolsonaro's "parallel cabinet". This group strongly supported the use of chloroquine/ hydroxychloroquine arguing that clinical experience is more important than rigid following of protocols.[10] While Raoult claimed that the superiority of his approach is rooted in profound clinical knowledge and compassion for patients, he has also a second line of defense. His collaborator, Yanis Roussel, who organized a highly successful campaign in favor of hydroxychloroquine therapy on social media, argued that the popular pressure for this drug's widespread use reflected a deep aspiration to democratize science (BERLIVET; LÖWY, 2020). Politicians aiming to base their interventions on scientific consensus, Roussel argued, often overlook the fact that the scientific establishment itself tends to be conservative. Advocates of scientific progress frequently find themselves compelled to contend for their ideas. With the battleground expanding to social media and Raoult's original article being shared tens of thousands of times, particularly through Elon Musk's Twitter account, the general public successfully democratized scientific knowledge (SCHULTZ; WARD, 2022).

The French debate surrounding the validity of Raoult's evidence on the efficacy of hydroxychloroquine, as indicated by sociologists, indeed played a role in educating the public on issues such as the use and limitations of randomized clinical trials. However, does engagement on social media truly lead to the democratization of science? Since the onset of the COVID-19 pandemic, actions like signing online petitions, watching videos on YouTube (notably, Raoult's views were predominantly disseminated in France through his videos), 'liking' Facebook pages, or retweeting health-related messages from a celebrity's account have been equated by some observers with new forms of patient/citizen activism, while politicians who endorsed the use of hydroxychloroquine, such as Bolsonaro, portrayed themselves as brave defenders of the people's interests against the perceived stifling views of experts. This strategy echoes previous approaches for example, to justify rejection of the scientific consensus on climate change (ORESKES; CONWAY, 2011). However, rather than constituting a movement for the democratization of science, support for untested and potentially harmful therapies promoted by populist politicians[11]had the opposite effect it suppressed debates over the social and political foundations of science. Activism focused on environmental or health-related issues operates

[10] The activity of MPV was analysed by Kenneth Camargo, in his in depth study of the "denialism" of Brazilian doctors (CAMARGO, 2024).

[11] When he was a MP, Bolsonaro was enthusiastic promoter of an untested cancer drug, fosfoetanolamina ("phospho") (SILVA; GONÇALVES, 2020).

differently. It influences policy primarily by revealing that there is no such thing as value-free expertise grounded solely in neutral, technical considerations.[12] Such activism is grounded in a deep engagement with core scientific issues. It enhances a public understanding how precisely science works and what are its strengths and limits, a goal advocated already by the pioner the sociology of scientific knowledge, Ludwik Fleck (LÖWY, 2016).

Countering individualistic or politicized approaches contrary to scientific knowledge health regulatory agencies and technical bodies within the MoH played a decisive role against non-evidence-based assumptions in Brazil. It's crucial to note that Anvisa has never endorsed the use of hydroxychloroquine, chloroquine, or ivermectin as effective treatments for COVID-19 (ANVISA, 2020a, 2020b).

Given the overwhelming demands during the COVID-19 epidemic in Brazil Anvisa faced challenges initiating strategies to monitor adverse effects and undesired events. When public discourse suggested a potential "preventive" or "therapeutic" role of hydroxychloroquine and chloroquine against COVID-19, the Brazilian population rushed to acquire these drugs. Anvisa responded swiftly by placing both drugs on the list of medicines under dispensing control to prevent shortages (ANVISA, 2020a).

Critiques against the distribution of the "COVID Kit" emerged within the Ministry of Health itself, notably from the National Committee for Technology Incorporation (Conitec). Conitec serves as an advisory board regulating the incorporation, exclusion, or alteration of medicines, health products and procedures in the country.[13] According to the PCI report on COVID-19, there was clear interference in Conitec's work during the pandemic, including attempts to postpone meetings assessing the effectiveness of drugs in the "COVID Kit" The PCI's findings also uncovered a "Parallel Cabinet", an ad-hoc structure composed of physicians and professionals advising the Minister of Health in favor of hydroxychloroquine and other ineffective drugs. A report, "Brazilian Guidelines for Drug Treatment of Patients with COVID-19" (MS, 2021), based on the best scientific evidence available at the time, clearly indicated the ineffectiveness of the "COVID Kit".

Despite numerous failed attempts to have Conitec's report approved by its plenary[14], this only happened at the end of 2021 after a public consultation. Notably, representatives of the Ministry of Health and the Federal Council of Medicine voted against the report.[15] The former published a note in January 2022 not only disavowing Conitec's conclusions but also criticizing COVID vaccines (G1, 2022).

[12] See for example, on AIDS activism, Epstein (1998).

[13] CONITEC was created by Law Nº. 12.401 of April 28, 2011

[14] Record of this meeting available at: CANAL DA CONITEC. 6ª Reunião Extraordinária da Conitec dia 21/10/2021. Disponível em: https://www.youtube.com/watch?v=vUAtGcyS4bE.

[15] Voting in favor of the report's directive were representatives of the National Supplementary Health Agency (ANS), the National Council of Health Secretaries (Conass), the National Council of Municipal

Conclusion

At the beginning of the COVID-19 pandemic, hydroxychloroquine or chloroquine were perceived as a miracle treatment in France and Brazil. A cross-analysis of the trajectory of these drugs in the two countries displays the differences and similarities between reactions to the pandemic, but also tensions between democracy and science; the autonomy of patients and prescribers and proof of efficacy supported by evidence-based medicine. It also points to the exercise of power by liberal medicine in contrast to Public Health values.

Both in France and in Brazil, chloroquine and hydroxychloroquine, were initially enthusiastically embraced by many physicians and patients, despite early indications that their efficacy as anti-COVID treatment were not well-founded, and that these substances could produce serious adverse effects. Moreover, in the later stages of the pandemic, the use of this drug also attracted those opposed to COVID vaccines.

The trajectory of hydroxychloroquine in Brazil was, however, different from its trajectory in France because of the strength in Brazil, of a "denialist" view propagated by the Bolsonaro Administration who contested the validity of the scientific discourse and provoked controversies around scientific methods to advance political goals.

Debates on the autonomy of prescribers and of sick people were distorted by the Brazilian anti-democratic political regime by disinformation and, at the same time, by the increased vulnerability of patients. By consequence, an organized community of doctors claimed their right to prescribe hydroxychloroquine in name of their professional "autonomy" and their "duty" to cure their patients, in a clear opposition to the international consensus regarding the use of this drug.

In France the debate on hydroxychloroquine came to an end in September 2020, and later only a handful of "revisionist" physicians continued to prescribe this molecule. In addition, the hydroxchloroquine controversy ended with an official investigation and the sanctioning of its main protagonist, Didier Raoult. By contrast in Brazil, in a context of threats and lack of respect for public health institutions, the use of CLQ/HCQ as COVID-19 treatments eschewed public scrutiny and was not submitted to social control. "Early treatment" by CLQ/HCQ continued to be a part of the official discourse of the federal government until the end of the Bolsonaro Administration. The Brazilian government disregarded technical recommendations of the National regulatory Agency and the views of scientific authorities in Brazil and worldwide; its decisions continued to be guided exclusively by the recommendation of its own "parallel cabinet."

Health Secretaries (Conasems), the National Health Council (CNS), the Secretariat for Science, Technology, Innovation and Strategic Inputs (SCTIE), and the Secretariat for Health Surveillance (SVS).

Even the Senate's PCI report, which clearly displayed the irregularities in the use of CLQ/HCQ during the COVID-19 pandemic had practically no effect on government's course of action, a telling illustration of the observation that public health is above all a political science. Or as Rudolf Virchow put it in 1848: "Medicine is a social science, and politics nothing but medicine at a larger scale" (MACKENBACH, 2009).

Conflict of interest: the authors declare no conflict of interest.

REFERENCES

ABRASCO - ASSOCIAÇÃO BRASILEIRA DE SAÚDE COLETIVA. **DOSSIÊ ABRASCO**: Pandemia de COVID-19. Rio de Janeiro, RJ: Associação Brasileira de Saúde Coletiva, 2022.

AFP. Après un rapport accablant sur l'IHU de Marseille sous la direction de Didier Raoult, le gouvernement saisit la justice. **Le Monde.fr**, 5 set. 2022.

AFP. Essais cliniques à l'IHU de Didier Raoult : l'ANSM annonce des « investigations » sur de possibles « manquements à la réglementation ». **Le Monde.fr**, 21 jul. 2021.

ANVISA - AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. **Nota Técnica sobre Cloroquina e Hidroxicloroquina**. 2020a. Disponível em: https://www.gov.br/anvisa/pt-br/arquivos-noticias-anvisa/830json-file-1. Acesso em: 28 jan. 2024

ANVISA - AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. **Nota de esclarecimento sobre a ivermectina**. 10 jul. 2020b. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2020/nota-de-esclarecimento-sobre-a-ivermectina. Acesso em: 28 jan. 2024.

ANVISA - AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. **RESOLUÇÃO-RDC N 96, DE 17 DE DEZEMBRO DE 2008**. 17 dez. 2008. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/propaganda/legislacao/arquivos/8812json-file-1. Acesso em: 28 jan. 2024

AUDUREAU, W. Les arguments spécieux de Didier Raoult pour défendre son étude sur l'hydroxychloroquine. **Le Monde.fr**, 5 jun. 2023.

BAKER, P. et al. Trump's Aggressive Advocacy of Malaria Drug for Treating Coronavirus Divides Medical Community. **The New York Times**, 7 abr. 2020.

BANDEIRA, K. Aposta do governo Bolsonaro em cloroquina contra Covid-19 teve impacto na oferta de insumo para combate à malária entre ianomâmis. **Jornal O Globo**, 1 fev. 2023.

BENDIX, T. Jimmy Kimmel Calls Trump a 'Hydroxymoron'. **The New York Times**, 20 maio 2020.

BERLIVET, L.; LÖWY, I. Hydroxychloroquine Controversies: Clinical Trials, Epistemology, and the Democratization of Science. **Medical Anthropology Quarterly**, v. 34, n. 4, p. 525–541, dez. 2020.

BEZERRA, L. Endocrinologista de Brasília toma posse em academia de ciências. **Correio Brasiliense / Cidades DF**, 15 set. 2023.

BOSELEY, S.; DAVEY, M. Covid-19: Lancet retracts paper that halted hydroxychloroquine trials. **The Guardian**, 4 jun. 2020.

BOULWARE, D. R.; PULLEN, M. F.; BANGDIWALA, A. S.; PASTICK K. A.; LOFGREN, S. M.; OKAFOR, E. C.; SKIPPER, C. P.; NASCENE, A. A.; NICOL, M. R.; ABASSI, M.; ENGEN, N. W.; CHENG, M. P.; LABAR, D.; LOTHER, S. A.; MACKENZIE, L. J.; DROBOT, G.; MARTEN, N.; ZARYCHANSKI, R.; KELLY, L. E.; SCHWARTZ, I. S.; MCDONALD, E. G.; RAJASINGHAM, R.; LEE, T. C.; HULLSIEK, K. H. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. **The New England Journal of Medicine**, v. 383, n. 6, p. 517–525, 6 ago. 2020.

BRASIL. SENADO FEDERAL. **Relatório Final da Comissão Parlamentar de Inquérito da Pandemia (Instituída pelos Requerimentos nos 1.371 e 1.372, de 2021**. Brasilia (DF): Senado, 2021.

CAMARGO, K. Disputed expertise and chaotic disinformation: COVID-19 and denialist physicians in Brazil. **Transcultural Psychiatry**, p. 13634615231213835, 17 jan. 2024.

CANAL DA CONITEC. 6ª Reunião Extraordinária da Conitec dia 21/10/2021. Disponível em: https://www.youtube.com/watch?v=vUAtGcyS4bE. Acesso em: 30 ago. 2024.

CASCELLA, M.; RAJNIK, M.; ALEEM, A.; DULEBOHN, S. C.; DI NAPOLI, R. **Features, Evaluation, and Treatment of Coronavirus (COVID-19)**. Treasure Island (FL): StatPearls Publishing, 2023.

CAVALCANTI, A. B.; CAVALCANTI, A. B.; ZAMPIERI, F. G.; ROSA, R. G.; AZEVEDO, L. C. P.; VEIGA, V. C.; AVEZUM, A.; DAMIANI, L. P.; MARCADENTI, A.; KAWANO-DOURADO, L.; LISBOA, T.; JUNQUEIRA, D. L. M.; DE BARROS E SILVA, P. G. M.; TRAMUJAS, L.; ABREU-SILVA, E. O.; LARANJEIRA, L. N.; SOARES, A. T.; ECHENIQUE, L. S.; PEREIRA, A. J.; FREITAS, F. G. R.; GEBARA, O. C. E.; DANTAS, V.C.S.; FURTADO, R. H. M.; MILAN, E. P.; GOLIN, N. A.; CARDOSO, F. F.; MAIA, I. S.; HOFFMANN FILHO, . R.; KORMANN, A. P. M.; AMAZONAS, R. B.; BOCCHI DE OLIVEIRA, M. F.; SERPA-NETO, A.; FALAVIGNA, M.; LOPES, R. D.; MACHADO, F. R.; BERWANGER, O; COALITION COVID-19 BRAZIL I INVESTIGATORS.

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. **The New England Journal of Medicine**, v. 383, n. 21, p. 2041–2052, 19 nov. 2020.

COLLECTIF CALL. Recherche clinique à l'IHU de Marseille: «En l'absence de réaction des institutions, les graves manquements constatés pourraient devenir la norme». **Le Monde**, 20 ago. 2023.

COLLUCCI, C. Estudo feito em Manaus aponta que alta dose de cloroquina está associada a mais mortes. **Valor Econômico**, 11 abr. 2020.

CONSELHO FEDERAL DE MEDICINA. **PROCESSO-CONSULTA CFM nº8/2020– PARECER CFM nº 4/2020**. Disponível em: https://sistemas.cfm.org.br/normas/visualizar/pareceres/BR/2020/4. Acesso em: 28 jan. 2024.

CNS - CONSELHO NACIONAL DE SAÚDE. Nota Pública: CNS alerta sobre os riscos do uso da Cloroquina e Hidroxicloroquina no tratamento da Covid-19. Publicado em 21 de maio de 2020. Disponível em: https://conselho.saude.gov.br/ultimas-noticias-cns/1194-nota-publica-cns-alerta-sobre-os-riscos-do-uso-dalica-cns-alerta-sobre-os-riscos-do-uso-da%20chloroquine%20and%20hydroxychloroquine%20in%20the%20treatment%20of%20COVID-21. Acesso em: 28 jan. 2024.

COQ-CHODORGE, C.; PASCARIELLO, P. Une inspection étrille les dérives autoritaires et médicales de l'IHU de Didier Raoult. **Mediapart**, 7 jul. 2022.

DAVEY, M. Unreliable data: how doubt snowballed over Covid-19 drug research that swept the world. **The Guardian**, 4 jun. 2020.

EPSTEIN, S. **Impure Science: AIDS, Activism, and the Politics of Knowledge**. [s.l.] University of California Press, 1998.

FALAVIGNA, M.; COLPANI, V.; STEIN, C.; AZEVEDO, L. C. P.; BAGATTINI, A. M.; BRITO, G. V.; CHATKIN, J. M.; CIMERMAN, S.; CORRADI, M. F. D. B.; CUNHA, C. A. D.; MEDEIROS, F. C.; OLIVEIRA JUNIOR, H. A.; FRITSCHER, L.; GAZZANA, M. B.; GRÄF, D. D.; MARRA, L. P.; MATUOKA, J. Y.; NUNES, M. S.; PACHITO, D. V.; PAGANO, C. G. M.; PARREIRA, P. C. S.; RIERA, R.; SILVA, A. JÚNIOR; TAVARES, B. M.; ZAVASCKI, A. P.; ROSA,,R. G.; DAL-PIZZOL, F. Guidelines for the pharmacological treatment of COVID-19. The task force/consensus guideline of the Brazilian Association of Intensive Care Medicine, the Brazilian Society of Infectious Diseases and the Brazilian Society of Pulmonology and Tisiology. **Revista Brasileira de Terapia Intensiva**, v. 32, n. 2, 2020.

FDA. **FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems**. 2020. Disponível em: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-

against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Acesso em: 28 jan. 2024.

FIOLET, T.; GUIHUR, A.; REBEAUD, M. E.; MULOT, M.; PEIFFER-SMADJA, N.; MAHAMAT-SALEH, Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. **Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases**, v. 27, n. 1, p. 19–27, jan. 2021.

FLOSS, M. et al. Linha do tempo do "tratamento precoce" para Covid-19 no Brasil: desinformação e comunicação do Ministério da Saúde. **Interface - Comunicação, Saúde, Educação**, v. 27, p. e210693, 9 dez. 2022.

G1. **Ministério da Saúde diz que hidroxicloroquina é segura, mas vacinas não; nota técnica contraria OMS e cientistas**. Publicado em 22 de janeiro de 2022. Disponível em: https://g1.globo.com/saude/coronavirus/noticia/2022/01/22/ministerio-da-saude-diz-que-hidroxicloroquina-e-segura-mas-vacinas-nao-nota-tecnica-contraria-oms-e-cientistas.ghtml. Acesso em: 28 jan. 2024.

GAUTRET, P.; LAGIER, J. C.; PAROLA, P.; HOANG, V. T.; MEDDEB, L.; MAILHE, M.; DOUDIER, B.; COURJON, J.; GIORDANENGO, V.; VIEIRA, V. E.; TISSOT DUPONT, H.; HONORÉ, S. COLSON, P.; CHABRIÈRE, E.; LA SCOLA, B.; ROLAIN, J. M.; BROUQUI, P.; RAOULT, D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. **International Journal of Antimicrobial Agents**, v. 56, n. 1, p. 105949, 1 jul. 2020.

ISAC. **Official statement from International Society of Antimicrobial Chemotherapy (ISAC)**. Andreas Voss, ISAC President. April 3rd-2020. Disponível em: https://www.isac.world/news-and-publications/official-isac-statement. Acesso em: 28 jan. 2024.

LAMONTAGNE, F.; STEGEMANN, M.; AGARWAL, A.; AGORITSAS, T.; SIEMIENIUK, R.; ROCHWERG, B.; BARTOSZKO, J.; ASKIE, L.; MACDONALD, H.; AL-MASLAMANI, M.; AMIN, W.; DA SILVA, A. R. A.; BARRAGAN, F. A. J.; BAUSCH, F. J.; BURHAN, E.; CECCONI, M.; CHACKO, B.; CHANDA, D.; DAT, V. Q.; DU, B.; GEDULD, H.; GEE, P.; HAIDER, M.; NERINA, H.; HASHIMI, M.; JEHAN, F.; HUI, D.; HUNT, B. J.; ISMAIL, M.; KABRA, S.; KANDA, S.; KAWANO-DOURADO, L.; KIM, Y. J.; KISSOON, N.; KRISHNA, S.; KWIZERA, A.; LISBOA, T.; LEO, Y. S.; MAHAKA, I.; HELA, M.; MIGLIORI, G. B.; MINO, G.; NSUTEBU, E.; PSHENICHNAYA. N.; QADIR, N.; RANGANATHAN, S. S.; SABZWARI, S.; SARIN, R.; SHANKAR-HARI, M.; SHARLAND, M.; SHEN, Y.; SOUZA, J. P.; TSHOKEY, T.; UGARTE, S. UYEKI, T.; VENKATAPURAM, S.; WACHINOU, A. P.; WIJEWICKRAMA, A.; VUYISEKA, D.; PRELLER, J.; BRIGNARDELLO-PETERSEN, R.; KUM, E.; QASIM, A.; ZERAATKAR, D.; OWEN, A.; GUYATT, G.; LYTVYN, L.;

JACOBS, M.; VANDVIK, P. O.; DIAZ, J. A living WHO guideline on drugs to prevent covid-19. **BMJ**, v. 372, p. n526, 2 mar. 2021.

LÖWY, I. Fleck the Public Health Expert: Medical Facts, Thought Collectives, and the Scientist's Responsibility. **Science, Technology, & Human Values**, v. 41, n. 3, p. 509–533, 1 maio 2016.

MACKENBACH, J. P. Politics is nothing but medicine at a larger scale: reflections on public health's biggest idea. **Journal of Epidemiology and Community Health**, v. 63, n. 3, p. 181–184, mar. 2009.

MEHRA, M. R.; DESAI, S. S.; RUSCHITZKA, F.; PATEL, A. N. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. **Lancet (London, England)**, p. S0140- 6736(20)31180–6, 22 maio 2020.

MILLION, M.; CORTAREDONA, S.; DELORME, L.; COLSON, P.; LEVASSEUR A.; TISSOT-DUPONT, H.; BENDAMARDJI, K.; LAHOUEL, S.; LA SCOLA, B.; CAMOIN-JAU, L.; FENOLLAR, L.; GAUTRET, P.; PAROLA, P.; LAGIER, J-C.; GENTILE, S.; BROUQUI, P.; RAOULT, D. Early Treatment with Hydroxychloroquine and Azithromycin: A 'Real-Life' Monocentric Retrospective Cohort Study of 30,423 COVID-19 Patients. **medRxiv**, 4 abr. 2023. Disponível em: https://www.medrxiv.org/content/10.1101/2023.04.03.23287649v1. Acesso em: 28 jan. 2024.

MS - MINISTÉRIO DA SAÚDE. CONITEC. **Diretrizes Brasileiras para Tratamento Medicamentoso Ambulatorial do Paciente com Covid-19**. Brasilia (DF): 2021.

MS - MINISTÉRIO DA SAÚDE. **Orientações do Ministério da Saúde para manuseio medicamentoso precoce de pacientes com diagnóstico da COVID-19**. Maio de 2020a. Disponível em: https://www.gov.br/saude/pt-br/centrais-de-conteudo/arquivos/orientacoes-manuseio-medicamentoso-covid19-pdf. Acesso em: 28 jan. 2024.

MS - MINISTÉRIO DA SAÚDE. **Ministério da Saúde amplia orientações para uso da cloroquina**. Junho de 2020b. Disponível em: https://www.gov.br/saude/pt-br/assuntos/noticias/2020/junho/ministerio-da-saude-amplia-orientacoes-para-uso-da-cloroquina-2. Acesso em: 28 jan. 2024.

MS - MINISTÉRIO DA SAÚDE. **Tratamento precoce contra Covid-19 é defendido por médicos para aumentar chance de cura**. Agosto de 2020c. Disponível em: https://www.gov.br/pt-br/noticias/saude-e-vigilancia-sanitaria/2020/08/tratamento-precoce-contra-covid-19-e-defendido-por-medicos-para-aumentar-chance-de-cura. Acesso em: 28 jan. 2024.

NUNES, M. Cientistas são ameaçados de morte; Fiocruz considera ataques inaceitáveis. **Correio Braziliense**, 17 abr. 2020.

ORESKES, N.; CONWAY, E. M. **Merchants of Doubt**: How a Handful of Scientists Obscured the Truth on Issues from Tobacco Smoke to Climate Change. Reprint edition ed. New York: Bloomsbury Publishing, 2011.

PAYET, M. Covid-19 : plus de 80 000 signatures pour le manifeste de Douste-Blazy pour la chloroquine. **leparisien.fr**, 3 abr. 2020.

PHILLIPS, D. Brazil loses second health minister in less than a month as Covid-19 deaths rise. **The Guardian**, 15 maio 2020.

PODER 360. Quem é de direita toma cloroquina, quem é de esquerda, Tubaína, diz Bolsonaro. Vídeo, 19 de maio de 2020. Disponível em: https://www.youtube.com/watch?v=UrD5nNfVNDE. Acesso em: 11 Nov 2023.

PRADELLE, A.; MAINBOURG, S.; PROVENCHER, S.; MASSY, E.; GRENET, G.; LEGA, J. C. Deaths induced by compassionate use of hydroxychloroquine during the first COVID-19 wave: an estimate. **Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie**, v. 171, p. 116055, 2 jan. 2024.

PRAZERES, L. Pesquisador de remédio tido como "milagroso" por bolsonaristas criou método usado em app da Saúde sob investigação. **O Globo**, 27 mar. 2021.

RAOULT, D. Didier Raoult : « Le médecin peut et doit réfléchir comme un médecin, et non pas comme un méthodologiste ». **Le Monde.fr**, 25 mar. 2020.

RECOVERY COLLABORATIVE GROUP; HORBY, P.; MAFHAM, M.; LINSELL, L.; BELL, J. L.; STAPLIN, N.; EMBERSON, J. R.; WISELKA, M.; USTIANOWSKI, A.; ELMAHI, E.; PRUDON, B.; WHITEHOUSE, T.; ELTON, T.; WILLIAMS, J.; FACCENDA, J.; UNDERWOOD, J.; BAILLIE, J. K.; CHAPPELL, L. C.; FAUST, S. N.; JAKI, T.; JEFFERY, K.; LIM, W. S.; MONTGOMERY, A.; ROWAN, K.; TARNING, J.; WATSON, J. A.; WHITE, N.; JUSZCZAK, E.; HAYNES, R.; LANDRAY, M. J. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. **The New England Journal of Medicine**, v. 383, n. 21, p. 2030–2040, 19 nov. 2020.

REUTERS. WHO says trials show malaria and HIV drugs don't cut Covid-19 hospital deaths. **The Guardian**, 4 jul. 2020.

ROF, G. L'étude de l'IHU accusée d'être un « essai sauvage » va être retirée par ses auteurs. **Le Monde.fr**, 2 jun. 2023.

RUGHINIȘ, C.; DIMA, L.; VASILE, S. Hydroxychloroquine and COVID-19: Lack of Efficacy and the Social Construction of Plausibility. **American Journal of Therapeutics**, v. 27, n. 6, p. e573–e583, 2020.

SAAG, M. S. Misguided Use of Hydroxychloroquine for COVID-19: The Infusion of Politics Into Science. **JAMA**, v. 324, n. 21, p. 2165–2176, 1 dez. 2020.

SANTOS-PINTO, C. D. B.; MIRANDA, E. S.; OSORIO-DE-CASTRO, C. G. S. O "kit-covid" e o Programa Farmácia Popular do Brasil. **Cadernos de Saúde Pública**, v. 37, p. e00348020, 22 fev. 2021.

SAYARE, S. He Was a Science Star. Then He Promoted a Questionable Cure for Covid-19. **The New York Times**, 12 maio 2020.

SCHULTZ, É.; ATLANI-DUAULT, L.; PERETTI-WATEL, P.; WARD, J. K. Does the public know when a scientific controversy is over? Public perceptions of hydroxychloroquine in France between April 2020 and June 2021. **Therapie**, v. 77, n. 5, p. 591–602, 2022.

SCHULTZ, É.; WARD, J. K. Science under Covid-19's magnifying glass: Lessons from the first months of the chloroquine debate in the French press. **Journal of Sociology**, v. 58, n. 1, p. 76–94, 1 mar. 2022.

SCIAMA, Y. Is France's president fueling the hype over an unproven coronavirus treatment? **Science**, 10 abr. 2020.

SENADO FEDERAL. Brasil poderia ter sido primeiro do mundo a vacinar, afirma Dimas Covas à CPI. **Agência Senado**, 27 de maio de 2021. Disponível em: https://www12.senado.leg.br/noticias/materias/2021/05/27/brasil-poderia-ter-sido-primeiro-do-mundo-a-vacinar-afirma-dimas-covas-a-cpi. Acesso em: 28 jan. 2024.

SILVA, R. D. F. C.; GONÇALVES, L. A. P. As pílulas do Messias: salvação, negação e política de morte em tempos de pandemia. **Physis: Revista de Saúde Coletiva**, v. 30, p. e300208, 24 jul. 2020.

SKIPPER, C. P.; PASTICK, K. A.; ENGEN, N. W.; BANGDIWALA, A. S.; ABASSI, M.; LOFGREN, S M.; WILLIAMS, D. A.; OKAFOR, E. C.; PULLEN, M. F.; NICOL, M. R.; NASCENE, A. A.; HULLSIEK, K. H.; CHENG, M. P.; LUKE, D.; LOTHER, S. A.; MACKENZIE, L. J.; DROBOT, G.; KELLY, L. E.; SCHWARTZ, I. S.; ZARYCHANSKI, R.; MCDONALD, E. G.; LEE, T. C.; RAJASINGHAM, R.; BOULWARE, D. R. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. **Annals of Internal Medicine**, v. 173, n. 8, p. 623–631, 20 out. 2020.

SUÁREZ-MUTIS, M. C.; MARTÍNEZ-ESPINOSA, F. E.; OSORIO-DE-CASTRO, C. G. S. **Nota técnica : orientações sobre o uso da Cloroquina para tratamento de pacientes infectados com SARS-CoV-2**. Instituto Oswaldo Cruz (IOC). Fundação Oswaldo Cruz, 2020.

VARGAS, M. Saúde prevê gastar R$ 250 milhões para pôr "kit-covid" em farmácias populares. **Estadão**, 11 dez. 2020.

WHO - WORLD HEALTH ORGANIZATION. **Coronavirus disease (COVID-19)**. Disponível em: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Acesso em: 26 jan. 2024.

WHO - WORLD HEALTH ORGANISATION. Drugs to prevent COVID-19: living guideline. Geneva, Switzerland. Publicado em 24 March 2023. Disponível em: https://www.who.int/publications/i/item/WHO-2019-nCoV-prophylaxes-2023.1. Acesso em: 30 ago. 2024.

WHO SOLIDARITY TRIAL CONSORTIUM. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. **New England Journal of Medicine**, v. 384, n. 6, p. 497–511, 2 dec. 2020.

WHO - WORLD HEALTH ORGANIZATION. **Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants**. Geneva: World Health Organization, 2011.

WIZIACK, J. Venda de cloroquina e ivermectina volta a subir com nova alta da Covid. **FOLHA DE S.PAULO**. Coluna Painel S.A. Publicado em 20 de junho de 2022. Disponível em: https://www1.folha.uol.com.br/colunas/painelsa/2022/06/venda-de-cloroquina-e-ivermectina-volta-a-subir-com-nova-alta-da-covid.shtml. Acesso em: 28 jan. 2024.

WONG, J. C. Hydroxychloroquine: how an unproven drug became Trump's coronavirus "miracle cure". **The Guardian**, 7 abr. 2020.

WRIGHT, L. **The Plague Year: America in the Time of Covid**. New York: Knopf, 2021.

Received on: 29/01/2024

Approved on: 02/04/2024