Current controversy

Hydroxychloroquine and COVID-19: critiquing the impact of disease public profile on policy and clinical decision-making

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ABSTRACT

The controversy surrounding the use of hydroxychloroquine (HCQ), an antimalarial drug, for COVID-19 has raised numerous ethical and policy problems. Since the suggestion that HCQ has potential for COVID-19, there have been varying responses from clinicians and healthcare institutions, ranging from adoption of protocols using HCQ for routine care to the conduct of randomised controlled trials to an effective system-wide prohibition on its use for COVID-19. In this article, we argue that the concept of 'disease public profile' has become a prominent, if not the sole, determinant in decision-making across various healthcare responses to the pandemic. In the case of COVID-19, the disease’s public profile is based on clinical and non-clinical factors that include contagiousness, clinical presentation and media coverage. In particular, we briefly examine the dangers of a heightened public profile in magnifying the inequality of diseases and undermining three key ethical concepts, namely (1) evidence-based practice, (2) sustainable allocation and (3) meaningful consent.

INTRODUCTION

The controversy surrounding the off-label use of hydroxychloroquine (HCQ) for COVID-19 is just one among numerous ethical problems raised by the current pandemic. In this article, we examine HCQ for COVID-19 as a case study in highlighting emerging ethical dilemmas. In particular, we document the role of disease public profile as the most prominent, if not the sole, determinant of decision-making that potentially undermines (1) evidence-based practice, (2) sustainable allocation and (3) meaningful consent. We acknowledge that although there are justifiable variations among national policies, practice guidelines and institutional protocols as a response to the outbreak, it remains important to identify both tacit and implicit values that underlie the decision-making in healthcare settings.

HCQ INDICATIONS

HCQ, along with chloroquine, belongs to a group of antimalarial agents known as 4-aminoquinolines. As more was learnt about HCQ’s immunomodulatory effects, its use expanded from the prevention and treatment of malaria to the treatment of various rheumatological and autoimmune conditions. HCQ putatively increases intracellular vacuolar pH to modify the processing of antigens within macrophages and other antigen-presenting cells. This mechanism likely pre-empts inflammatory responses that could be maladaptive and lead to the symptoms of autoimmune disease. Data from randomised controlled clinical trials (RCTs) have established the efficacy of HCQ for the treatment of specific rheumatological conditions such as systemic lupus erythematosus and rheumatoid arthritis.

A potential role of HCQ in the treatment of COVID-19 has been suggested. In vitro data have demonstrated activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), likely through the inhibition of nucleic acid synthesis, viral protein glycosylation, virus assembly, virus particle transport and viral release. Clinical data on its use in COVID-19 are sorely limited. A non-randomised open-label clinical study conducted in France included 26 patients treated with HCQ and 16 controls. Researchers reported a greater decline in viral load on day 6 of treatment compared with untreated patients, particularly when HCQ was combined with azithromycin. The conclusions of the study have been thoroughly scrutinised owing to its methodological limitations. In contrast, a small randomised controlled study in China that included 30 patients and compared HCQ with standard care did not demonstrate a difference in viral clearance on day 7 of treatment. Systematically collected data on clinical outcomes over a reasonable follow-up period have yet to be reported but may have emerged by the time of this publication. In the face of limited data, the US Food and Drug Administration (FDA) has opted to grant limited emergency use authorisation, though not approval, to the use of HCQ in the treatment of COVID-19.

HCQ as well as many other drugs being repurposed to treat COVID-19 are not without risk of serious adverse events, including potentially fatal cardiac abnormalities (eg, arrhythmias). These risks may be heightened in critically ill patients with comorbidities that place them at high cardiovascular risk.

In the wake of widespread use in healthcare facilities across the world, the Infectious Disease Society of America has issued recommendations to use HCQ only in the context of a clinical trial. The American Thoracic Society-led international task force issued guidelines of their own that suggested considering the use of HCQ for hospitalised patients with COVID-19 pneumonia on a case-by-case basis, taking into account shared decision-making, collection of valid data and the severity of the patient’s condition.
DISEASE AND PUBLIC PROFILE

Regulatory boards, healthcare institutions and clinicians are now involved in a contest on whether HCQ is appropriate for one medical condition but not for another. The pandemic demonstrates the role of COVID-19’s public profile in magnifying the inequality of diseases. Here, we discuss clinical and non-clinical factors that underpin disease public profile that potentially privileges one medical condition over others.

First, contagiousness is a key factor that causes one disease to be deemed or perceived as far more important than others. Contagiousness, including ease and mode of transmission, of a disease determines the imperatives to intervene.15 In the case of COVID-19, the transmission is through the transfer of respiratory droplets between persons who are in close contact (within 1 m). Other modes of COVID-19 transmission include direct contact with infected individuals, as well as contact with surfaces used or touched by the infected individual. Worse, studies have shown that SARS-CoV-2, the novel coronavirus causing COVID-19, has a higher transmissibility rates than other viruses such as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and 2009 H1N1.16 Concerns have also been raised regarding transmissions from asymptomatic and presymptomatic persons that are expected to challenge containment efforts.17 Thus, unlike in malaria and lupus, contagiousness in COVID-19 entails a sense of larger scale, more sense of urgency and greater threat.

Second, the clinical presentation (ie, acuity, prognosis and case-fatality rate) determines the perceived importance of some diseases over others. Accumulating clinical experience documented in case reports18–20 and relayed in anecdotes among treating clinicians contribute to the sense that patients may deteriorate rapidly and dramatically, making COVID-19 distinct from most viral types of pneumonia. The case-fatality rate for COVID-19 has varied widely, reflecting differences in multiple factors such as testing practices, containment efforts or demographic structure. Estimates have ranged from as low as 1.2% in Germany and 2.3% in China to as high as 9% in Spain and 11.9% in Italy.21 In contrast, the United States Centers for Disease Control and Prevention (CDC) has estimated that from 1 October 2019 to 4 April 2020, there have been 39–56 million cases of illness and 24 000–62 000 deaths from influenza, which translates to a case-fatality rate of only up to 0.2%.22

Third, media coverage is another factor that informs the inequality of disease conditions. Although media coverage of a disease is a non-clinical factor, it is correlated with the contagiousness and clinical presentation of the disease in question. Public profile due to media coverage is best exemplified by conditions in two extremes of perceived worthiness as a cause: breast cancer and (any type of) orphan disease. Breast cancer has a high public profile mainly due to effective awareness campaigns across the globe that often involve celebrities who encourage regular examination and support for research.23 On the other extreme are orphan diseases, so-called because they are so rare that drug companies are not inclined to adopt them to develop treatments. In the current scenario, lupus (and to some extent malaria) are closer to the orphan disease side of the spectrum and COVID-19 in the other extreme. Unlike breast cancer, the worthiness of COVID-19 as a cause is not due to any corporatised awareness campaign. Rather it is due to the 24/7 coverage, the grim picture in countries like Italy and Iran, the daily updates on incidence and fatality rates and the extreme social interventions (eg, lockdowns) among others.

Increased public profile in itself is not problematic, as some rare or unknown diseases have received increased research funding through this route. A famed example is the ‘ice bucket challenge’, involving celebrities dumping ice water on their heads to promote awareness of and research on amyotrophic lateral sclerosis, a rare motor neuron disease.24 The danger of increased public profile of disease is demonstrated by the tendency of public officials with no medical expertise, such as US President Donald Trump and French President Emmanuel Macron,25 to explicitly recommend drug treatments and prophylaxis against COVID-19. One harmful result of President Trump’s pronouncements is the death of a man from Arizona who ingested a cleaning cocktail that contains the same active ingredient as HCQ.26 Furthermore, increased public profile heightened by unfounded treatment recommendations have negatively impacted the academic and medical community, with scientific publications accelerating dramatically at the expense of academic rigour that validates the integrity of the research.27 As a result, several published articles have been retracted by elite medical journals The Lancet and The New England Journal of Medicine following revelations of questionable data sources.28

In the next three sections, we elaborate the ways in which one disease’s public profile, such as COVID-19’s, can become so extraordinary that it undermines evidence-based clinical practice, drives unsustainable resource allocation and authorises structural forms of coercive consent.

INSUFFICIENT EVIDENCE

The heightened public profile of disease appears to increase the imperative to resort to off-label treatments, both for therapeutic and prophylactic purposes. In the case of COVID-19, various drugs are proposed or currently under investigation as potential off-label treatments. However, at the time of this writing, there was still no standard of care. Off-label use refers to the use of treatment (medication or device) for regimens not stated in the approved labelling or package insert.29 Off-label use is considered a common practice and sometimes clinically appropriate in cases when there are no alternatives and potential benefits outweigh potential risks.30 However, off-label use has raised longstanding debates on whether it is morally justified. By its very definition, off-label use entails treatments that are not yet fully supported by evidence. In response to the potential harms of unproven treatments, national medical associations have stated some guidelines on off-label treatments. For example, the American Medical Association’s Code of Ethics states that off-label and other innovative treatments must be based on ‘sound scientific evidence and appropriate clinical expertise’.31 The Australian Medical Association similarly recommends that off-label use should be based on ‘sufficient evidence to support its efficacious and safe use and overall favourable harm:benefit ratio’.32 Although there are several morally justifiable reasons for off-label use in general clinical practice, our analysis focusses on the influence of disease public profile on the unapproved or emergency use of HCQ for COVID-19 without sufficient scientific evidence.

But what counts as scientific and/or sufficient evidence? Despite the good intentions of these practice guidelines, it seems that off-label use will remain in a ‘Catch-22’ situation given the contradicting regulations. On one hand, a common regulation states that drugs can only be used for indications of which they are approved by authorities such as the US FDA. On the other hand, drug authorities do acknowledge and to some extent permit the use of drugs for unapproved or unproven indications granted the best available evidence supports this unapproved use. If there were evidence deemed by authorities to be sufficient
to support use for the indication in question, this labelling would be approved and the use no longer off-label.

It is widely accepted that the strongest evidence for adopting a treatment comes from well-designed randomised controlled trials, or a meta-analysis of such well-designed trials if study designs are sufficiently similar. Anecdotes are powerful, but they have a limited ability to make fair comparisons between any two treatment options. Outside a controlled setting, observed differences in outcomes may be due to the differences in the treatments. But they are just as likely due to pre-existing differences in the risks of patients themselves for developing a poor outcome, and these are misattributed to the treatments received. Variables that are readily or quickly measured (eg, laboratory test results such as persistent detectability of viral particles) may be used to compare the two treatments, but they do not necessarily translate to the clinical outcomes that are directly experienced by patients (eg, resolution of symptoms, discharge and death). Thus, good clinical trial design, ideally including the randomisation of patients to different treatment arms, is the key to producing interpretable data that best inform the care of patients. However, when such data do not yet exist, clinicians nevertheless must make patient care decisions using the best available evidence.

Any evidence that falls short of an RCT can be classified into supported, suppositional and investigational.29 The classification relies on the availability of non-RCT evidence and expert opinion. Among the three, the investigational off-label use has the lowest level of certainty. At the time of this writing, a search in clinicaltrials.gov yielded 44 studies on the use of HCQ to prevent or treat COVID-19 in various stages ranging from prerecruitment to completed. Though there is much disagreement on the merits of HCQ as a treatment, most researchers and clinicians likely at least agree that equipoise exists. Though we are uncertain, the probability that HCQ works is at least enough to merit investigation through RCTs that will either affirm or debunk its role in care.

While awaiting the results of these RCTs, treating clinicians have taken a wide range of positions on the off-label use of HCQ in treating COVID-19. For the sake of this discussion, we can consider two: the treating clinician should consider the off-label use of HCQ in a closely monitored inpatient setting for patients at increased risk of an adverse outcome from COVID-19 versus the treating clinician should provide supportive care alone and not consider any targeted off-label therapy outside the context of an RCT.

The position to consider off-label use has been described as the compulsion to ‘just do it’,13 or the drive to do something rather than nothing. In contrast, the position to refrain from off-label use outside the context of an RCT has been presented as a necessary measure to protect patients from adverse consequences of treatment that might later prove to lack efficacy anyway.12 In this light, the position to offer and use HCQ off-label (ie, to ‘just do it’) may be perceived as instinctual or irrational. Nevertheless, it must be recognised that the position to refrain from off-label HCQ use to avoid serious adverse events from unproven therapy is based on an alternate instinct as well. The latter position instinctively presupposes that death from a serious adverse event from HCQ that is later proven ineffective for COVID-19 must be a worse outcome than death from COVID-19 if HCQ is later proven effective but was not tried. The former position presupposes the opposite. Given the heightened public profile of COVID-19, it is conceivable that some next of kin of deceased patients would find greater comfort or less regret in thinking, ‘We tried’, or, ‘We did everything we could’, whereas others by, ‘We did not know it could have worked’. However, when experts determine that off-label use outside of an RCT (of an agent that has enough potential to be investigated in an RCT) should be discouraged when managing an individual patient with their own preferences, they do make an inadvertent claim that one value or preference is objectively superior to another. However, these preference hierarchies are by nature subjective and, thus, requiring continued ethical scrutiny.

UN Sustainable Allocation

The impact of COVID-19’s public profile on evidentiary concerns trickles down to issues regarding resource allocation based on government policies, hospital protocols and norms of clinical practice. In the case of HCQ, one issue is regarding the fair distribution of the drug among its indicated uses (eg, malaria and lupus) and off-label use for COVID-19.

As a consequence of the interest in HCQ for COVID-19, no doubt fuelled by President Trump’s endorsement,34 demand for the drug has skyrocketed.15 The precarity of supply has prompted diverging responses at the level of the state and healthcare organisations or at least varying opinions from different stakeholders on how to manage the scarcity. A patient with lupus has reportedly been issued a letter by her healthcare network explaining that the HCQ supply was being conserved in favour of those critically ill with COVID-19.36 The COVID-19 Global Rheumatology Alliance highlighted the major risk of disease flare and organ damage in patients with lupus who might be unable to refill their HCQ prescriptions.8 In their statement, they discouraged off-label use until further efficacy data emerge in favour of its use in COVID-19 and the supply is bolstered. At least until before the US FDA’s emergency authorisation, certain states had opted to restrict dispensing HCQ for conditions outside the proven indications.35

As various expert panels and bodies have highlighted the threat to the HCQ supply for lupus patients generated by HCQ use in the treatment of COVID-19,8 media reports of unusual prescribing patterns on the part of healthcare providers have emerged.33 There is suspicion that physicians, dentists and other licensed providers are issuing themselves or family members prescriptions of HCQ to stockpile them, ostensibly to take them prophylactically or to use them should they develop symptoms. The magnitude of this practice is unclear, but it does pose an ethical concern that treatment practices surrounding patients hospitalised with COVID-19 are being influenced by an allocation problem generated by some prescribers hoarding for themselves or significant others who are not or only mildly symptomatic.

Bioethical debates regarding medical resource allocation generally involve two main competing positions: the maximising utility view and the equity view. The former follows the utilitarian precept of promoting the greatest good for the greatest number of persons,38 whereas the latter highlights the need to redress social injustice and socioeconomic inequalities that result in unfair distribution of goods.29 Using the utility view, the competition among diseases means that governments and health institutions should focus on the disease where treatment will result in the greatest good for the greatest number. The key criticism against utility view is that the greatest good is often at the expense of a vulnerable minority, whether in terms of persons or diseases. In contrast, the equity view recognises that certain groups of people are already at a disadvantage. The equity view can be useful in demonstrating that in a public health crisis, some disease conditions are vulnerable to neglect as resources...
are diverted disproportionately to the disease that receives high public attention. In the example of breast cancer, there has been a growing criticism against the ‘pink ribbon’ campaign as receiving excessive attention at the expense of other types of cancer.40

The case of HCQ for COVID-19 demonstrates a problematic allocation of resources that cuts across various domains of healthcare. Intensive care unit beds, mechanical ventilators and human resources are now largely diverted toward COVID-19.41 Arguably, diverting resources toward a highly contagious disease during a pandemic is justifiable. However, such a strategy can have unintended harmful consequences. For example, health experts warn against the surge of polio, measles and other infectious diseases as COVID-19 efforts trigger the suspension of worldwide vaccination campaigns.42 A patient with lupus who is unable to fill their HCQ prescription could end up requiring hospital care from a life-threatening lupus flare, but be unable to receive optimal care from a system now primed to focus on COVID-19. Hence, the trend of allocating resources, including HCQ, toward COVID-19 is not only disproportionate but may also prove to be unsustainable or counterproductive in the long run.

**COERCIVE CONSENT**

The public profile of a disease similarly impacts the creation of undue influence on patient consent to participate in research trials. When the US FDA granted emergency authorisation for HCQ, there was concern that offering off-label therapy outside RCTs leads to a squandered opportunity to enrol these patients in them.32 If off-label therapy is offered outside the context of an RCT, there is reduced motivation or incentive to participate in one. However, if they could be persuaded to participate, their outcomes would provide clarity to the treating clinician in their care of future patients.

In bioethics, consent is deemed meaningful and informed if the person giving it is ‘competent to act, receives a thorough disclosure, comprehends the disclosure, chooses voluntarily and consents to the intervention’.43 Competence, comprehension and voluntariness can be compromised by coercion and undue influence, which are two overlapping concepts. Although coercion is generally understood as direct use of threat of violence, undue influence occurs when there is an excessive and inappropriate reward to obtain compliance.44 For some authors, coercion can occur when there is a substantially asymmetric power dynamic between the physician/researcher and the patient/participant. Patients and potential research participants may be coerced to consent if they fear they have something to lose by not complying with the request. In a less pessimistic light, coercion may occur when patients overly trust their physicians so that a physician’s invitation to participate may be viewed as a recommendation rather than a request.45 Concerns regarding potential coercion of participants have been demonstrated in clinical trials for cancer treatments,46 HIV cure47 and treatment for psychiatric disorders,48 among others. Authors argue that therapeutic clinical trials tend to collapse the two roles of a clinician as providing clinical care and performing research, and this collapse can contribute to patients’ misconception that participation in the trial is a matter of necessity if not an obligation.49

Clinicians and future patients with COVID-19 would be best served by the participation of current patients with COVID-19 in these RCTs. Nevertheless, one of the cornerstones of modern ethical codes governing clinical research is preserving the participant’s ability to provide meaningful consent.49 50 Withholding an Off-label agent (with sufficient potential to warrant RCT investigation) in the course of care functions as an inducement to consent to join the study. Study participation might entail being randomised to placebo (ie, supportive care alone) when the patient would otherwise not have agreed to be. Understandably, in practice, many RCTs often involve incentives, but these are closely scrutinised precisely because of the risk of compromising meaningful consent. A conflict, therefore, arises between future patients on one side and the current patient whose only access to off-label therapy is through an RCT. Although the informative findings of an RCT might serve the ‘greater good’, this must be carefully weighed against protecting the meaningful consent of patients being recruited.

The controversy surrounding HCQ further demonstrates that undue influence and coercion can be structural. Wider social, economic and political contexts can undermine understanding and voluntariness as components of consent.46 Structural and indirect forms of coercion can be shaped by social disparities that perpetuate unequal access to resources that help people make healthier and more informed choices.41 For example, US reports show that the pandemic has highlighted the disparity in access to technology and online information from reputable websites such as the US Centers for Disease Control and Prevention,42 leading to hoax and conspiracy sites that promote unfounded and harmful COVID-19 treatments.43 Moreover, structural forms of coercion are demonstrated by the ways in which the public profile of COVID-19 magnifies the impact of political, social and institutional influence on participants consenting to ongoing HCQ trials. On a political level, some state leaders, such as President Trump and President Macron,25 have been vocal in their confidence with HCQ, putting demands on researchers and clinicians who are already under intense pressure to develop treatments for COVID-19. Consequently, political faith on a treatment that is not supported by evidence has spurred greater society’s demand to have access to HCQ,25 either as a prophylaxis or treatment against COVID-19. The hype may play a role in influencing patients’ decision to participate in trials or to seek treatments that are at best not proven to be effective or worst associated with potentially fatal side effects.

**CONCLUSIONS**

In this article, we argued that the case of HCQ being touted as potential COVID-19 treatment demonstrates the dangers of a disease’s public profile becoming the overarching influence in healthcare decision-making. The public profile of a disease, which is based on a combination of clinical features and media coverage, not only magnifies the inequality of diseases but also potentially undermines the ethical concepts of evidence-based medicine, sustainable allocation of resources and meaningful consent. Given the rapid progression of the pandemic, we acknowledge the need for quick clinical and policy responses. Although we do not advocate for a particular outcome of decision-making, we wish to highlight the need for ethical deliberation to make explicit the values that are informing widespread and immediate responses to the pandemic. We need to strike a balance between matters of urgency and matters of equity, with some medical conditions becoming vulnerable to neglect and ethical concepts being dismissed, as resources and attention are diverted towards COVID-19.

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