Hidden in Plain Sight: COVID-19 and the Great Off-Label Hypocrisy

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"Hydroxychloroquine and azithromycin, taken together, have a real chance to be one of the biggest game changers in the history of medicine."[1]
Former President Donald Trump,
Mar 19, 2020

"The nail has virtually been put in the coffin of hydroxychloroquine."[2]
Dr. William Schaffner,
Vanderbilt University,
May 11, 2020

ABSTRACT

The COVID-19 pandemic response provoked intense conflict between direct-care physicians and corporate medical, pharmaceutical, political, and media leadership over the freedom to enquire into and apply the best available treatments. The best example involved off-label use of drugs like hydroxychloroquine (HCQ) and ivermectin (IVM). Instead of considering the totality of evidence for and against any therapy, a corpus of favorable evidence for early-use effectiveness of these drugs was buried, under the guise of "Follow the Science." This early-use evidence, which is currently hidden in plain sight, must be resurrected.

Background

Famous descriptors in the history of COVID-19 include: "Flatten the Curve,""Operation Warp Speed," and the benumbing mantra, "Follow the Science." However, in the summer of 2020, for those of us tasked with making recommendations to direct caregivers of COVID-19 patients, no headline deepened our dilemma more than Dr. Anthony Fauci's declaration on July 31, 2020 , in testimony before the House Select Subcommittee on the Coronavirus Pandemic, that evidence for the benefit of hydroxychloroquine (HCQ) in treating COVID-19 was "flawed."[3] With that one word, he dismissed a large observational study from Detroit, which demonstrated the benefit of HCQ in hospitalized patients,[4] and simultaneously upended the standard for actionable medical evidence, which exists "Beyond Randomized Controlled Trials."[5]

"Flawed" set the stage to *arbitrarily omit favorable evidence*, and "follow the science" became follow the leader. Actionable evidence shrank to a non-scientific binary: *randomized clinical trial (RCT) only—others need not apply*.

HCQ had been buried early on by many declared experts, one confidently asserting that "the nail has virtually been put in the coffin of hydroxychloroquine."[2] This presaged the official reversal of a preliminary emergency use authorization (EUA] support from the Food and Drug Administration (FDA) one month later. Precipitous declarations of evidence or lack thereof—a sitting president all but declaring HCQ a miracle drug,[1] followed by a leading expert in infectious diseases all but declaring HCQ as dead,[2] brought internal conflict and undermined public trust.

The FDA had issued an EUA for HCQ on Mar 28, 2020, based on its powerful in-vitro and in-vivo antiviral activity, substantial immunomodulatory properties, proposed five-day dosing regimen, extensive familiarity worldwide , extraordinary safety profile, and favorable early-use effectiveness.[6] Direct-care physicians responded with off-label use, which is both legal and common, encompassing 20 to 30 percent of prescriptions in the U.S.

But HCQ suddenly became ignominious, and "off label" became "off limits." Swarming behavior took hold, and pallbearers were appointed. The HCQ-for-COVID-19 funeral procession made its way to the evidence graveyard, and early-use evidence was "buried."[7]

Why This Campaign against Repurposed Drugs?

Were there *no flaws* in Dr Fauci's categorical statement? He indicted HCQ evidence because it was not based on the RCT. But according to Dr. Thomas Frieden, former Director of the Centers for Disease Control and Prevention (CDC), "RCTs have substantial limitations."[5] And the inconvenient truth holds that early-use studies looking at HCQ have included dozens of RCTs. Therefore, fairness and disclosure demand serious reconsideration of all RCTs in this matter—all of which have substantial limitations.[5] In fact, all evidence is inherently flawed.

Was there not even a "scintilla of evidence" regarding HCQ? This is the common-law principle of the minutest relevant evidence, which may require a decision by a jury. On the very day of Dr. William Schaffner's death-knell pronouncement on HCQ, Dr. Harvey Risch of Yale submitted far more than a scintilla of evidence for early use for publication. This could have been "ramped up immediately,"[6] but the damage had already been done.

Was there *no memory* that a possible HCQ shortage was being proffered as a very early reason not to use off-label prescribing? But by April 2020 there was optimism, given a large manufacturing base internationally and the abundance of raw materials, that global demand for HCQ could be met.[8]

Was there *no apprehension* over currently backed anti-virals for early use losing their effectiveness[9] or driving mutational resistance?[10]

Was there *no nuance* based on the pathophysiology of disease and the timing of treatment decisions—in this case the fact that COVID-19 is a biphasic illness characterized by an early viral/outpatient phase followed by the later immune/hospital phase?[11]

Was there *no obligation* to debate that the logical fallacy of conflation has been committed on a massive scale? The obsession over HCQ use being less effective in hospitalized patients was misleadingly conflated with favorable evidence for early use to make the drug appear to be ineffective in all settings.

Was there *no hypocrisy* over the safety record of HCQ in a six-decade-long clinical experience with outpatient administration for malaria, lupus, and rheumatoid arthritis, *without* routine screening electrocardiograms?[12] Or over why off-label was "permitted" for steroids in hospitalized COVID patients before any RCT, or over why physicians who treat patients with long COVID are turning to off-label use of drugs for diabetes, addiction, and autonomic dysfunction?[13] These inconsistencies and double standards expose the FDA's hypocrisy with regard to HCQ and IVM.

Was there not *disregard for the logical fallacy of circular reasoning*? This holds that "A is true, because B is true " and that "B is true because A is true." In the case of HCQ use, "misinformation" is "non-evidence based" and "non-evidence based" is "misinformation."[14] But the only misinformation lies in the definition of misinformation, resting on the logical fallacy of conflation, where any use of HCQ is branded misinformation without giving its due to early-use/outpatient evidence. This is fallacy begetting fallacy.

Was there *no curiosity* as to why five-day outpatient treatment courses of Paxlovid™ and Legevrio™, which received EUAs in December 2021, were selected? This is strangely similar to an optimized dosing design of the five-day formulations of HCQ.[15] It is reasonable to conclude that HCQ science provided the scientific premise for optimal treatment to occur in the viral phase.

To date, Paxlovid has not demonstrated effectiveness in hospitalized COVID patients.[16] This in contrast to the "flawed"[3] Detroit study of hospitalized COVID patients, which found that: "In the multivariable Cox regression model of mortality using the group receiving neither hydroxychloroquine or azithromycin as the reference, treatment with hydroxychloroquine alone decreased the mortality hazard ratio by 66% ($p<0.001$), and hydroxychloroquine + azithromycin decreased the mortality hazard ratio by 71% ($p<0.001$)."[4]

There is in fact a corpus of knowledge about the use of HCQ, IVM, and other off-label drugs, for example, at c19hcq.org,[17] c19IVM.org[18] and earlycovidcare.org.[19] Groups of scientists have relentlessly catalogued and updated results of every study (including both early and late treatment use) on HCQ and other orphaned medications such as IVM, since February 2020. Hundreds of thousands of COVID-19 patients have been studied by thousands of researchers in dozens of countries, leading to official endorsement of these repurposed medications as legitimate treatment options in many locations world-wide.

If studies catalogued on these sites are not credible science, then what are they? Pseudoscience? Bad science? Politicized science? Rather, these sites are like compelling exhibits in an evidentiary hearing, but instead of being subjected to scrutiny, they are being hidden in plain sight.

The IVM controversy, previously highlighted in this journal,[20] has come into view as a legal matter. Most recently, the U.S. Court of Appeals for the Fifth Circuit ruled on the side of three physicians, by reinstating their right to sue the FDA over the agency's campaign of warning patients not to take the drug. The FDA had condescendingly told the public on X (Twitter) that they are not animals: "You are not a horse."[21-23]

The court, in response, ruled: "The FDA is not a physician."[21,22]

Those who dismiss the websites c19hcq.org and c19ivm.org have stated that the scientists who compile them are anonymous. But corporate leadership within too many medical societies, healthcare systems, guideline organizations, pharmaceutical bodies, governmental entities and national media outlets have refused to seriously consider hundreds of studies, including multiple RCTs, the authors of which *are* known, or the meta-analyses provided. Feedback is invited on these sites. Those who argue that content cannot be judged on its merits because of anonymous authorship need to re-read the history of *Common Sense* by Thomas Paine.

But then this is not about science. If it were, there would be no fear to debate this corpus of knowledge out in the open, using the scientific method.

Why This Matters: the Threat to Science

The controversy over COVID-19 treatment shows the threat to the scientific method from a new orthodoxy: *Medicine as political purpose*.[24]

In the pre-pandemic era most physicians would not have dreamt that political purpose could become a major potential bias influencing scientific discovery or backing a COVID-19 therapeutic horse on anything other than the deep tradition of the scientific method. To wit, in the summer of 2020, I attempted to do what I had always done over four decades as an infectious disease consultant: direct my colleagues to the totality of evidence for and against any therapy (such as those contained in these online summaries) and support them in consultation with their patients to make therapeutic decisions. But something strange began to emerge that summer, when determinative debate was scuttled, where the physician as expert was undermined, and where the physician as authority was usurped.

The standard for medicine must be restored to the apolitical rules of the racetrack but the question remains as to whether and why these rules were abandoned with respect to HCQ and IVM in 2020.

In the courtroom of the scientific method, a merger of inductive and deductive thinking is precedent; questioning, argumentation and minority dissent is welcomed; skepticism of one's own position is robust; and premature judgment is suspended. In *that* courtroom the burden of proof needs to rest on medical corporatists, as the prosecution, to prove to the jury of practicing physicians that the HCQ/IVM corpus of knowledge for early use is guilty of being *unfavorable* to the patient and can therefore be summarily dismissed. If it *is* favorable, then there is a duty to disclose this exculpatory evidence, followed by the duty to explain why early in an international emergency—without either vaccines or consensus-based outpatient therapies—that broad off-label authority became selectively off limits.

Evidentiary justice demands a full hearing. The great hypocrisy against early-use HCQ/IVM will put the nail in the coffin of trust. "Off-label" prescribing authority is on shaky ground overall for the next pandemic, if early-use HCQ evidence (hidden in plain sight) is allowed to die in the present one.

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