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A flawed Covid-19 study gets the White House's attention — and the FDA may pay the price

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Reprints[4]

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Studies in thousands of people on multiple continents now show the malaria drug hydroxychloroquine does not help patients hospitalized with Covid-19 live longer. But on Tuesday the White House, based on a new study[5] that outsiders greeted with deep skepticism, disagreed.

Now the Food and Drug Administration again risks being pulled into an ugly political fracas over whether to permit more patients to be treated with the drug. It is a debate that threatens to undermine the agency's credibility when it needs it perhaps more than ever.

"The FDA cannot afford another misstep if it wants to maintain credibility with American people, which is going to be so essential when doing a broad vaccine program, should we identify a safe and effective vaccine for Covid," said Luciana Borio, who served as the FDA's acting chief scientist from 2017 to 2019.

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At the root of the conflict is the fundamental principle that the FDA uses to evaluate drugs. Decisions are based almost entirely on what is known as a randomized controlled trial, in which patients are randomly assigned to receive a treatment or not. Other types of studies have, again and again, failed to deliver accurate information about medicines' benefits and risks, and are used sparingly in making medical decisions. Three randomized studies have now shown no benefit for hydroxychloroquine in hospitalized patients.

The study that sparked the latest controversy was anything but randomized. Not only was it not randomized, outside experts noted, but patients who received hydroxychloroquine were also more likely to get steroids, which appear to help very sick patients with Covid-19. That is likely to have influenced the central finding of the Henry Ford study: that death rates were 50% lower among patients in hospitals treated with hydroxychloroquine.

On Monday, President Trump, who has long been enthusiastic about hydroxychloroquine and even took the drug himself, tweeted about the results, saying that Democrats had politicized the drug and that the FDA should should "Act Now"[7]. The president's trade adviser, Peter Navarro, told reporters that Henry Ford had asked the FDA to issue a new emergency use authorization for

the drug. The agency had previously revoked hydroxychloroquine's authorization[8] on June 15, based on evidence it was not effective.

Experts were taken aback by the developments.

"The medical community has come to the inescapable conclusion that hydroxychloroquine is not effective at treating Covid-19 infections," said Steven Nissen, a cardiologist at the Cleveland Clinic and a longtime clinical trialist. "Peter Navarro is not a scientist, he is the president's trade representative. He should not be advising the public on matters of health."

Nissen and Borio say observational studies simply cannot be used to determine whether a medicine is effective. Again and again they have been wrong. In one famous example, estrogen replacement therapy after menopause was thought to have benefits in preventing heart and other problems; large studies showed this was not the case. In another, a knee surgery for arthritis was shown to have no benefits over medical care.

A paper that showed that hydroxychloroquine was potentially harmful, which was published in The Lancet in May, was met with similar criticism. It was eventually withdrawn over questions about the validity of its data.

Observational studies are often used to decide what ideas to test in randomized studies, to make sure that results from randomized studies translate to the real world, and to detect side effects.

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But, puzzlingly, Henry Ford has applied for authorization to use hydroxychloroquine "for a clearly defined list of clinical uses, including use in clinical trials," the system said in a statement.

"We owe it to our patients and our communities to do everything we can to provide safe, effective, affordable treatments, and we will continue to collaborate toward meaningful solutions that address this deadly disease."

Evidence that hydroxychloroquine does not help hospitalized patients — the use in its original emergency use authorization, which was designed to allow doctors to access a national stockpile of the drug — is mounting.

One study, the RECOVERY study conducted in the U.K.,[10] compared 1,542 patients on a particularly high dose of the drug to 3,132 control patients and found no difference in how long patients lived. A second, conducted by the National Institutes of Health, also found no benefit from hydroxychloroquine at higher doses.

Yet, in his interview with the White House press pool, Navarro argued that the studies so far were based on "bad science" and that the Henry Ford data were evidence enough. He argued that the drug appears to work when given earlier in the disease course than it was in the large randomized studies. He said that rescinding the FDA authorization had "a tremendously negative effect" on two things.

"One is the ability for American people to use this medicine to protect themselves," Navarro said, "and, two, the ability for hospitals, like the Detroit hospital system, to recruit patients for the kind of randomized blind clinical trials that everybody wants to settle once and for all the questions of efficacy and safety."

It is not clear how the FDA's decision to rescind the emergency authorization for hydroxychloroquine affected either. Doctors can prescribe any drug for any use, and conducting a clinical trial requires a different type of approval from the FDA. It is clear that granting a new emergency use authorization based on an observational study would go against decades of experience by medical researchers and regulators around the globe.

A huge amount of scientific attention has been focused on hydroxychloroquine. An analysis[11] Monday by STAT and AppliedXL, a computational journalism company, found that 1 in 6 clinical trials started for Covid-19 involved hydroxychloroquine or a similar drug, chloroquine.

Said Nissen: "The sooner we stop talking about hydroxychloroquine, the sooner we can focus attention on more promising therapies."

About the Author Reprints[4]

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