IN DEPTH

The Germans Trias i Pujol University Hospital near Barcelona, Spain, where a prevention trial with hydroxychloroquine took place.

PHOTO: FELIPE DANA/ASSOCIATED PRESS

COVID-19

Big studies dim hopes for hydroxychloroquine

Amid politicization and scandal, a disappointing scientific picture is emerging

By **Kai Kupferschmidt**

Through the fog of alleged misconduct, hope, hype, and politicization that surrounds hydroxychloroquine, the malaria drug touted as a COVID-19 treatment, a scientific picture is now emerging.

Praised by presidents as a potential miracle cure and dismissed by others as a deadly distraction, hydroxychloroquine was spared a seeming death blow last week. On 4 June, after critics challenged the data, *The Lancet* suddenly retracted a paper that had suggested the drug increased the death rate in COVID-19 patients (see p. 1167), a finding that had stopped many clinical trials in their tracks. But now three large studies, two in people exposed to the virus and at risk of infection and the other in severely ill patients, show no benefit from the drug. Coming on top of earlier smaller trials with disappointing findings, the new results mean it's time to move on, some scientists say, and end most of the trials still in progress.

"It just seems like we are ignoring signal after signal," says Eric Topol, director of the Scripps Translational Science Institute. U.S. President Donald Trump's promotion of it led to a scientific "obsession" with hydroxychloroquine despite thin evidence for its promise, he says. "We'd be better off shifting our attention to drugs that might actually work." Peter Kremsner of the University of Tübingen agrees hydroxychloroquine "certainly isn't a wonder drug." The new results left him "wrestling" with the question of whether to proceed with two hydroxychloroquine trials, one in hospitals and the other in patients with milder illness at home.

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Hydroxychloroquine and its sister drug chloroquine have been used against malaria and other diseases for decades. The first evidence that they might work against SARS-CoV-2 came from test tube data. Since then, hundreds of trials have been launched around the globe. Scientists are trying the drugs in low doses and high doses; alone or combined with the antibiotic azithromycin, the antiviral compound favipiravir, or other drugs; and in patients with mild or severe disease, health care workers, pregnant women, and people living with HIV.

On 5 June, researchers in the United Kingdom announced the results from the largest trial yet, Recovery, in a press release. In a group of 1542 hospitalized patients treated with hydroxychloroquine, 25.7% had died after 28 days, compared with 23.5% in a group of 3132 patients who had only received standard care. "These data convincingly rule out any meaningful mortality benefit," wrote the investigators, who ended the study early and promised to publish the full results as soon as possible.

The results are persuading some doctors to stop using the drug for COVID-19. "The Recovery trial, in addition to the signals from other studies we have received so far, are enough to convince me to not offer hydroxychloroquine to hospitalized patients," Nahid Bhadelia, a physician at Boston Medical Center, wrote in an email. Martin Landray of the University of Oxford, one of Recovery's principal investigators, agrees: "If you, your spouse, your mother gets admitted to hospital and is offered hydroxychloroquine, don't take it," he says.

But some scientists say they want to see the full data before making up their minds. About one in four patients died in both arms of the study, Kremsner notes—a very high rate, suggesting they were gravely ill when treatment started. Nicholas White of Mahidol University in Bangkok, who also studies hydroxychloroquine, agrees the full data need evaluation. "But overall, it's very

unlikely, in my view right now sitting here, that anything's going to change," he says.

Another hope for hydroxychloroquine, that it might prevent people exposed to the virus from getting sick, also faded last week when David Boulware of the University of Minnesota, Twin Cities, and colleagues published the results of the largest study to date of this strategy, called post-exposure prophylaxis (PEP). The researchers sent either hydroxychloroquine or a placebo by mail to 821 people who had been in close contact with a COVID-19 patient for more than 10 minutes without proper protection. They reported in *The New England Journal of Medicine* that 12% of the people who took the drug went on to develop COVID-19 symptoms, versus 14% in a placebo group, a difference that was not statistically significant.

A second large PEP trial has come up empty as well, its leader tells *Science*. Carried out in Barcelona, Spain, that study randomized more than 2300 people exposed to the virus to either hydroxychloroquine or the usual care. There was no significant difference between the number of people in each group who developed COVID-19, says Oriol Mitjà of the Germans Trias i Pujol University Hospital. Mitjà says he has submitted the results for publication.

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Martin Landray, University of Oxford

The data are important because they come from large randomized trials. So far, most data came from small trials or case series. A meta-analysis of 24 such studies published in the *Annals of Internal Medicine* concluded there was "insufficient and often conflicting evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19."

The new findings raise questions about whether to stop other trials. Most are much smaller than Recovery, and thus less powerful; their outcomes are unlikely to change many minds. And continuing the trials may prevent researchers from testing drugs with a better chance of working and robs patients of the chance to try those. Landray says the World Health Organization (WHO) is now likely to end the hydroxychloroquine arm of its large COVID-19 treatment trial, named Solidarity. "I think the decision is pretty obvious," he says. WHO says it is considering the issue.

There is one exception. Many researchers agree that a good case can be made for continuing to test whether hydroxychloroquine can prevent infection if given to people just in case they get exposed to the virus, for instance on the job at a hospital—a strategy called pre-exposure prophylaxis (PrEP). "You have a much better chance of preventing something with a weak drug than you have of curing a fully established infection," says White, who runs one of the largest PrEP trials. He notes that doxycycline, an antibiotic, has long been used in malaria prophylaxis. "We would never treat anybody with it, it's too weak. But it's a very good prophylactic."

Landray, however, is on the fence about continuing prophylaxis trials: "I suspect it's one of these decisions where there isn't a right or wrong." It's an important question, Bhadelia says, because an effective PrEP drug could have a major impact on the pandemic. Hydroxychloroquine, a cheap and widely available drug, is one of the few compounds that could fit the bill.

But the *Lancet* paper, despite its retraction, will make it more difficult to continue current trials, White laments. Published on 22 May, the study claimed, supposedly based on data from 96,000 patients around the world, that hydroxychloroquine and chloroquine, whether given alone or in combination with another drug, caused a steep increase in deaths. That led many regulatory agencies to ask scientists to halt their trials and make sure they were not harming their patients. Recovery and Solidarity were temporarily halted but resumed after a safety committee took a look at the data.

Many other trials are still on pause. U.K. regulators, for instance, have asked for a raft of additional safeguards, says Joseph Cheriyan, a clinical pharmacologist at Cambridge University Hospital and principal investigator of a PrEP trial in health care workers. That study already excluded patients who take any one of several dozens of drugs, but Cheriyan says regulators have asked for more changes, which will set the trial back weeks. And despite the *Lancet* retraction, the alarming headlines about the drug's risks have made it much more difficult to convince people to participate in a trial, White says. "I just think these trials have been really badly damaged and some of them may never restart."

The problem for scientists is that there's such a rush to find treatments for the rapidly spreading virus, Mitjà says: "The pressure is immense." Yet that shouldn't stop researchers from properly analyzing data and making carefully considered decisions, White says. "We don't always have to act today," he says. "Let's not panic." ■

COVID-19

Authors, elite journals under fire after major retractions

Editors, co-authors missed warning signs, critics say

By **Charles Piller** *and* **John Travis**

Last month, Mandeep Mehra, Amit N. Patel, and Sapan Desai were riding high, with shared co-authorships on major new papers in *The Lancet* and *The New England Journal of Medicine* (*NEJM*) and an influential preprint. Drawing on what appeared to be a vast patient data trove from hospitals around the world, the papers delivered seemingly definitive news about whether already approved drugs were safe for COVID-19 patients, or effective against the disease.

Now, the two journal papers have been retracted, the preprint taken down, and Patel's academic affiliation severed. The three physician-scientists are under the microscope as a shocked scientific community evaluates what may be the first major episode of research fraud in the pandemic. The journals are receiving withering criticism for what some call a failure of editorial processes and peer review. The retractions are "unnerving and disturbing," says Leigh Turner, a bioethicist at the University of Minnesota, Twin Cities. The rush to publish on COVID-19 has exposed a lack of rigor that has reached "elite journals at the top of the academic pyramid," he says.

The retracted *NEJM* paper "had external peer review and statistical review, as well as scientific and manuscript editing," an *NEJM* spokesperson says. *The Lancet* did not comment on its review process. Neither journal notes submission or acceptance dates for papers, but a spokesperson for Mehra says reviews for each paper took about 1 month.

By publishing only author retraction statements, the journals "didn't show any self-reflection, any introspection," Turner says. To him, the case also raises a bigger question about how much access to key data each journal should require—and whether all co-authors should have full access to a data set. "The less access they have, the greater the chances that there will be

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