



# Covid-19: WHO halts hydroxychloroquine trial to review links with increased mortality risk

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The BMJ

The World Health Organization has halted testing of hydroxychloroquine in patients with covid-19 after a study found that the drug was linked with an increased risk of mortality and heart arrhythmias.

The study, published in the *Lancet*,<sup>1</sup> included more than 96 000 patients admitted to hospital with covid-19 in six continents from December 2019 to April 2020. Compared with those who did not receive the drugs, people treated with chloroquine or hydroxychloroquine (with or without a macrolide) showed an increased risk of dying in hospital and de novo ventricular arrhythmia.

The researchers have said that these drug regimens should not be used to treat covid-19 outside clinical trials and called for urgent confirmation of the findings from randomised clinical trials.

Hydroxychloroquine has been backed by the US president, Donald Trump, who said that it had shown “very, very encouraging early results,” that it was “not going to kill anybody,”<sup>2</sup> and that he had actually taken it for weeks to prevent himself from getting the virus.

The *New York Times* has reported that shareholders and executives tied to Trump stand to profit if hydroxychloroquine becomes an accepted treatment, and the president himself has a personal financial interest in Sanofi, which makes a branded version of the drug.<sup>3</sup>

## Temporary pause

WHO has been testing potential covid-19 treatments through its Solidarity Trial, involving over 400 hospitals in 35 countries. However, after the *Lancet* paper was published, WHO’s director general, Tedros Adhanom Ghebreyesus, said that the hydroxychloroquine arm of the trial had been halted.

Speaking at a daily briefing on the pandemic on 25 May,<sup>4</sup> he said, “The executive group has implemented a temporary pause of the hydroxychloroquine arm within the Solidarity Trial while the data is reviewed by the Data Safety Monitoring Board.” He added that, alongside the new research, the reviewers would also look at data collected so far in the Solidarity Trial—“in particular, robust randomised available data, to adequately evaluate the potential benefits and harms from this drug.”

However, recruitment for the RECOVERY trial at the University of Oxford, UK, which will test six potential covid-19 treatments including hydroxychloroquine, has continued. A statement<sup>5</sup> from the chief investigators said that the team had worked

closely with the Medicines and Healthcare Products Regulatory Agency to review the situation and that it had confirmed in writing that “it is acceptable to allow continued randomisation into the hydroxychloroquine arm of the trial.”

The statement added, “The RECOVERY trial provides the best and most rapid opportunity to produce robust information on the overall effects of hydroxychloroquine on the risk of death from covid-19.”

## In-hospital mortality

The *Lancet* study included 96 032 patients (mean age 53.8 years, 46.3% women), of whom 14 888 were in the treatment groups: 1868 who received chloroquine, 3783 who received chloroquine with a macrolide, 3016 who received hydroxychloroquine, and 6221 who received hydroxychloroquine with a macrolide. Meanwhile, 81 144 patients were in the control group. All patients had either recovered or died (10 698 in hospital) by April 2020.

The authors reported, “After controlling for multiple confounding factors, when compared with mortality in the control group (9.3%), hydroxychloroquine (18.0%; hazard ratio 1.335 (95% confidence interval 1.223 to 1.457)), hydroxychloroquine with a macrolide (23.8%; 1.447 (1.368 to 1.531)), chloroquine (16.4%; 1.365 (1.218 to 1.531)), and chloroquine with a macrolide (22.2%; 1.368 (1.273 to 1.469)) were each independently associated with an increased risk of in-hospital mortality.

“Compared with the control group (0.3%), hydroxychloroquine (6.1%; 2.369 (1.935 to 2.900)), hydroxychloroquine with a macrolide (8.1%; 5.106 (4.106 to 5.983)), chloroquine (4.3%; 3.561 (2.760 to 4.596)), and chloroquine with a macrolide (6.5%; 4.011 (3.344 to 4.812)) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalisation.”

Stephen Evans, professor of pharmacoepidemiology at the London School of Hygiene and Tropical Medicine, said that the study “is one of the better ones, both in its size and its general conduct,” although he noted that excluding patients who started treatment more than 48 hours after diagnosis or when using mechanical ventilation may have led to a bias against finding possible benefits of the drugs, as the same criteria could not be applied to the control group.

Daniel Levin, a statistician at the University of Dundee, also raised concerns over excluding from the analysis patients who had not died or recovered by the cut-off date.

He said, “If the treatment groups had either a true positive or negative effect on mortality, thereby leading to a longer duration of hospitalisation for the treatment or control groups respectively, this exclusion could result in the true effect being diluted, potentially beyond the point of reversal . . .

“Given the strict safety measures present in all clinical trial protocols, to use the results of a well designed observational study to halt an ongoing clinical trial ought to raise eyebrows. To use a flawed one should not go unchallenged.”

The study was funded by the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women’s Hospital in Boston, Massachusetts. Two of the authors reported interests, including personal fees from drug companies and being the founder of a healthcare company, Surgisphere Corporation, which has developed a diagnostic tool for covid-19.

Surgisphere also provided some funding and statistical help for the research.

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