

The Lancet doubts over hydroxychloroquine study see WHO restart trials

June 3 2020, by Paul Ricard, Kelly MacNamara



Both hydroxychloroquine and chloroquine can produce potentially serious side effects, particularly heart arrhythmia

The WHO announced Wednesday the resumption of its hydroxychloroquine trials after The Lancet cast doubt over a large-scale

study it published last month that led to temporary suspension of testing of the drug.

The medical journal has issued an "expression of concern" over a large-scale study of hydroxychloroquine and chloroquine that led to the World Health Organization to pause clinical trials of the former as a potential treatment for COVID-19.

The WHO said hydroxychloroquine trials would restart after a safety review found there was no reason to modify the trial.

The *Lancet* acknowledged "important" questions over the research into the anti-viral drugs, after dozens of scientists issued an open letter raising concerns about its methodology and the underlying data, which was provided by the US-based firm Surgisphere.

"Although an independent audit of the provenance and validity of the data has been commissioned by the authors not affiliated with Surgisphere and is ongoing, with results expected very shortly, we are issuing an Expression of Concern to alert readers to the fact that serious scientific questions have been brought to our attention," The *Lancet* said Tuesday.

While an expression of concern is not as severe as a journal withdrawing a published study, it signifies that the research is potentially problematic.

The observational study looked at records for 96,000 patients and concluded that treatment with hydroxychloroquine, which is normally used to treat arthritis, and chloroquine, an anti-malarial, showed no benefit in the treatment of COVID-19 and even increased the likelihood of patients dying in hospital.

"We are now fairly confident, not having seen any differences in

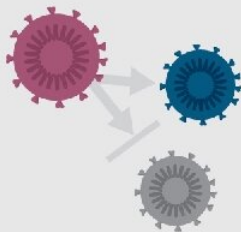
mortality, that the data safety monitoring committees of both solidarity and recovery have recommended that the trial can continue," the WHO's Soumya Swaminathan told a press briefing on Wednesday.

France was among the countries to also halt COVID-19 treatment with hydroxychloroquine.

The study whipped up fresh controversy over hydroxychloroquine, which has been endorsed by public figures—including US President Donald Trump—despite concerns over side effects and a lack of evidence that it is effective.

COVID-19 drugs

Remdesivir: attacks virus replication



Antiviral: stops or slows the virus's ability to make copies of itself

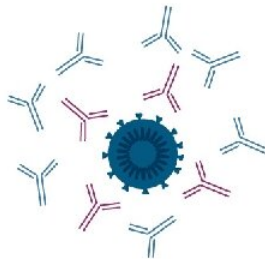
Approved for emergency use in the US, Japan and South Korea after positive clinical trials

Hydroxychloroquine, antimalarial and anti-autoimmune disease, has been also studied for potential antiviral effects

Testing has been suspended in several countries pending safety concerns

Other drug strategies under investigation

Boost the immune response

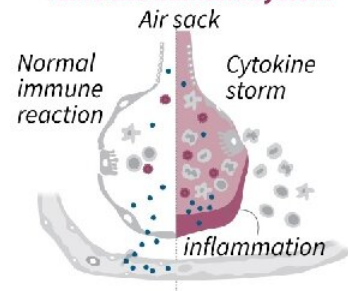


Identify **antibodies** that respond to SARS-CoV-2 and deploy them

Promising antibodies found in research by biotech companies such as **AbCellera** in Canada, **Regeneron**, US

Testing of blood **plasma** from recovered patients also ongoing

Tame the immune system



Work against the **cytokine storm** when the immune system goes into overdrive

Swiss company Roche investigating the use of a rheumatoid arthritis drug **tocilizumab**, which inactivates cytokine proteins that accelerate the immune response

Another arthritis drug, **sarilumab**, also being tested

Sources: newsscientist.com/covid19treatmentguidelines.nih.gov/gilead.com

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Graphic on the main drug strategies approved or under investigation in the battle against COVID-19. South Korea joins the US and Japan in approving emergency use of remdesivir against COVID-19.

Data concerns

The study's authors, led by Mandeep Mehra of the Brigham and Women's Hospital in the United States, looked at data from hundreds of hospitals between December and April and compared those who received either of the two drugs—with or without an antibiotic—with a control group.

It followed numerous smaller studies that suggested hydroxychloroquine is ineffective in treating COVID-19.

However, in an open letter last week, a group of scientists raised "both methodological and data integrity concerns" about it.

These included a lack of information about the countries and hospitals that contributed to the data provided by Chicago-based healthcare data analytics firm Surgisphere.

While The Lancet corrected a discrepancy in data from Australia, the authors on Friday said they stood by their findings and announced an independent review.

But concerns over the data continued, and this week the *New England Journal of Medicine* also issued an expression of concern over another study using the Surgisphere database that looked at cardiovascular drugs and COVID-19.

Mehra, lead author on both studies, said Wednesday the goal of the independent auditors was to "verify the source data and assess the accuracy of the database and the authors' findings".

"I have routinely underscored the importance and value of randomised, clinical trials and articulated that such trials will be necessary before any conclusions can be reached," his statement said, adding that the use of observational data was "an intermediary step".

Surgisphere head Sapan Desai, a co-author on the research, said the firm "stands behind the integrity of our studies and our scientific researchers, clinical partners, and data analysts".



Among the most outspoken critics of The Lancet study has been French professor Didier Raoult, whose own work has been at the forefront of promoting

hydroxychloroquine and has also been subject to criticisms over methodology

'Serious reflection'

Among the most outspoken critics of *The Lancet* study has been French professor Didier Raoult, whose own work has been at the forefront of promoting hydroxychloroquine and has also been subject to criticisms over methodology.

But other critics, like Francois Balloux of University College London, raised concerns over the way the study was conducted even though they are sceptical the drugs themselves would work as a treatment for COVID-19.

Peter Horby, professor of emerging infectious diseases and global health at Oxford University said the controversy should spark "serious reflection" over the quality of the peer review process.

"Scientific publication must above all be rigorous and honest. In an emergency, these values are needed more than ever," he said.

He added, however, that decisions to halt clinical trials on the basis of an observational study were "completely unjustified".

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