

Retractions and controversies over coronavirus research show that the process of science is working as it should

July 7 2020, by Mark R. O'brian

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

Methods We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (as defined or sustained or transient ventricular tachycardia or ventricular fibrillation).

Findings 96 032 patients (mean age 53·8 years, 46·3% women) with COVID-19 were hospitalised during the study period and met the inclusion criteria. Of these patients, 18 668 were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 77 364 patients were in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple confounding factors (eg, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% CI 1·22–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·318–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated with an increased risk of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6·5%; 2·365, 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; 1·751, 1·270–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretation We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased

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Brigham and Women's Hospital
Heart and Vascular Center and
Harvard Medical School,
Boston, MA, USA
(Prof M R Mehra MD);
Surgisphere Corporation,
Chicago, IL, USA (S S Desai MD);
University Heart Center,
University Hospital Zurich,
Zurich, Switzerland
(Prof F Ruschitzka MD);
Department of Biomedical
Engineering, University
of Utah, Salt Lake City, UT, USA
(A N Patel MD); and HCA
Research Institute, Nashville,
TN, USA (A N Patel)
Correspondence to:
Prof Mandeep R Mehra, Brigham
and Women's Hospital Heart and
Vascular Center and Harvard
Medical School, Boston,
MA 02115, USA
mmehra@bwh.harvard.edu

The paper published in The Lancet claimed that hydroxychloroquine increased risk of death in COVID-19 patients, but was retracted when other scientists discovered the data used for the study was unreliable. Credit: [The Lancet/Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel](https://www.thelancet.com)

Several high-profile papers on COVID-19 research have come under fire

from people in the scientific community in recent weeks. Two articles addressing the safety of certain drugs when taken by COVID-19 patients were [retracted](#), and researchers are calling for the retraction of a third paper that evaluated behaviors that [mitigate coronavirus transmission](#).

Some people are viewing the retractions as an [indictment of the scientific process](#). Certainly, the overturning of these papers is bad news, and there is plenty of blame to go around.

But despite these short-term setbacks, the scrutiny and subsequent correction of the papers actually show that [science](#) is working. Reporting of the pandemic is allowing people to see, many for the first time, the messy business of scientific progress.

Scientific community quickly responds to flawed research

In May, two papers were published on the safety of certain drugs for COVID-19 patients. The first, published in the *New England Journal of Medicine*, claimed that a particular heart medication [was in fact safe for COVID-19 patients](#), despite previous concerns. The second, published in *The Lancet*, claimed that the antimalarial drug [hydroxychloroquine increased the risk of death](#) when used to treat COVID-19.

The Lancet paper caused the World Health Organization to briefly [halt studies investigating hydroxychloroquine](#) for COVID-19 treatment.

Within days, over 200 scientists signed an [open letter](#) highly critical of the paper, noting that some of the findings were simply implausible. The database provided by the tiny company Surgisphere—whose website is no longer accessible—was unavailable during peer review of the paper or to scientists and the public afterwards, preventing anyone from

evaluating the data. Finally, the letter suggested that it was unlikely this company was able to obtain the hospital records alleged to be in the database when no one else had access to this information.

By early June, both [the *Lancet*](#) and [New England Journal of Medicine](#) articles were retracted, citing concerns about the integrity of the database the researchers used in the studies. A retraction is the withdrawal of a published paper because the data underlying the major conclusions of the work are found to be seriously flawed. These flaws are sometimes, but not always, due to intentional scientific misconduct.

The urgency to find solutions to the COVID-19 pandemic certainly contributed to the publication of sloppy and possibly fraudulent science. The quality control measures that minimize the publication of bad science failed miserably in these cases.

Imperfect and iterative

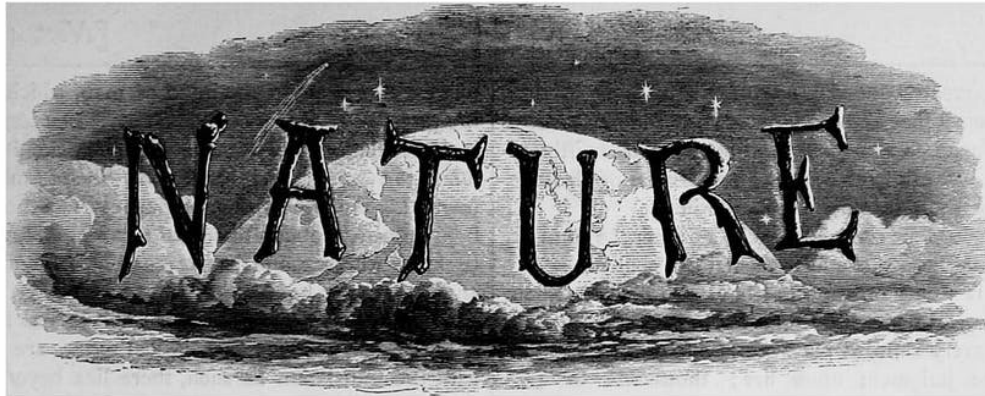
The retraction of the hydroxychloroquine paper in particular drew immediate attention not only because it placed science in a bad light, but also because [President Trump had touted the drug](#) as an effective treatment for COVID-19 despite the lack of strong evidence.

Responses in the media were harsh. The *New York Times* declared that "[The pandemic claims new victims: prestigious medical journals.](#)" The Wall Street Journal accused the *Lancet* of "[politicized science](#)," and the Los Angeles Times claimed that the retracted papers "[contaminated global coronavirus research.](#)"

These headlines may have merit, but perspective is also needed. [Retractions are rare](#) – only about 0.04% of published papers are withdrawn—but scrutiny, update and correction are common. It is how science is supposed to work, and it is happening in all areas of research

relating to SARS-CoV-2.

Doctors have learned that the disease [targets numerous organs](#), not just the lungs as was initially thought. Scientists are still working on understanding whether COVID-19 patients [develop immunity](#) to the disease. And to close the case on hydroxychloroquine, [three new large studies](#) published after the *Lancet* retraction indicate that the malaria drug is indeed ineffective in preventing or treating COVID-19.



A WEEKLY ILLUSTRATED JOURNAL OF SCIENCE

*"To the solid ground
Of Nature trusts the mind which builds for aye."*—WORDSWORTH

THURSDAY, NOVEMBER 4, 1869

NATURE: APHORISMS BY GOETHE

NATURE! We are surrounded and embraced by her: powerless to separate ourselves from her, and powerless to penetrate beyond her.

Without asking, or warning, she snatches us up into her circling dance, and whirls us on until we are tired, and drop from her arms.

She is ever shaping new forms: what is, has never yet been; what has been, comes not again. Everything is new, and yet nought but the old.

We live in her midst and know her not. She is incessantly speaking to us, but betrays not her secret. We constantly act upon her, and yet have no power over her.

The one thing she seems to aim at is Individuality; yet she cares nothing for individuals. She is always building up and destroying; but her workshop is inaccessible.

Her life is in her children; but where is the mother? She is the only artist; working-up the most uniform material into utter opposites; arriving, without a trace of effort, at perfection, at the most exact precision, though always veiled under a certain softness.

Each of her works has an essence of its own; each of her phenomena a special characterisation: and yet their diversity is in unity.

She performs a play; we know not whether she sees it herself, and yet she acts for us, the lookers-on.

Incessant life, development, and movement are in her, but she advances not. She changes for ever and ever, and rests not a moment. Quietude is inconceivable to her, and she has laid her curse upon rest. She is firm. Her steps are measured, her exceptions rare, her laws unchangeable.

She has always thought and always thinks; though not as a man, but as Nature. She broods over an

all-comprehending idea, which no searching can find out.

Mankind dwell in her and she in them. With all men she plays a game for love, and rejoices the more they win. With many, her moves are so hidden, that the game is over before they know it.

That which is most unnatural is still Nature; the stupidest philistinism has a touch of her genius. Whoso cannot see her everywhere, sees her nowhere rightly.

She loves herself, and her innumerable eyes and affections are fixed upon herself. She has divided herself that she may be her own delight. She causes an endless succession of new capacities for enjoyment to spring up, that her insatiable sympathy may be assuaged.

She rejoices in illusion. Whoso destroys it in himself and others, him she punishes with the sternest tyranny. Whoso follows her in faith, him she takes as a child to her bosom.

Her children are numberless. To none is she altogether miserly; but she has her favourites, on whom she squanders much, and for whom she makes great sacrifices. Over greatness she spreads her shield.

She tosses her creatures out of nothingness, and tells them not whence they came, nor whither they go. It is their business to run, she knows the road. Her mechanism has few springs—but they never wear out, are always active and manifold.

The spectacle of Nature is always new, for she is always renewing the spectators. Life is her most exquisite invention; and death is her expert contrivance to get plenty of life.

She wraps man in darkness, and makes him for ever long for light. She creates him dependent upon the earth, dull and heavy; and yet is always shaking him until he attempts to soar above it.

B

Since the beginning of scientific publishing, peer review has helped weed out bad science, but public discourse between researchers has easily played as big a role. Credit: [Public Domain](#)

Science is self-correcting

Before a paper is published, it undergoes peer review by experts in the field who recommend to the journal editor whether it should be accepted for publication, rejected or reconsidered after modification. The reputation of the journal is dependent on high-quality peer review, and once a [paper](#) is published, it is in the public domain, where it can then be evaluated and judged by other scientists.

The publication of the *Lancet* and the *New England Journal of Medicine* papers failed at the level of peer review. But scrutiny by the [scientific community](#)—likely spurred on by the public spotlight on coronavirus research—caught the mistakes in record time.

The hydroxychloroquine article published in *The Lancet* was retracted only 13 days after it was published. By contrast, it took 12 years for the *Lancet* to retract the fraudulent article that [incorrectly claimed vaccinations cause autism](#).

It is not yet known whether these papers involved deliberate scientific misconduct, but mistakes and corrections are common, even for top scientists. For example, [Linus Pauling](#), who won the Nobel Prize for discovering the structure of proteins, later published an [incorrect structure of DNA](#). It was subsequently corrected by [Watson and Crick](#).

Mistakes and corrections are a hallmark of progress, not foul play.

Importantly, these errors were exposed by other scientists. They were not uncovered by some policing body or watchdog group.

This back-and-forth between academics is foundational to science. There is no reason to believe that scientists are more virtuous than anyone else. Rather, the mundane human traits of curiosity, competitiveness, self-interest and reputation come into play before and after publication are what allow science to regulate itself. A model based on robust evidence emerges while the weaker one is abandoned.

Living with uncertainty

From high school classes and textbooks, science seems like a body of well-known facts and principles that are straightforward and incontrovertible. These sources view science in hindsight and often make discoveries seem inevitable, even dull.

In reality, scientists learn as they go. Uncertainty is inherent to the path of discovery, and success is not guaranteed. [Only 14% of drugs and therapies](#) that go through human clinical trials ultimately win FDA approval, with less than a 4% success rate for cancer drugs.

The process of science generally takes place below the radar of public awareness, and so this uncertainty is not generally in view. However, Americans are [paying close attention](#) to the COVID-19 pandemic, and many are, for the first time, seeing the sausage as it is being made.

Although the recent retractions may be unappetizing, medical science has been very successful over the long run. Smallpox has been eradicated, infections are treated with antibiotics rather than amputation and pain management during surgery has advanced well beyond biting on

a stick.

The system is by no means perfect, but it is pretty darned good.

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