Controversial papers in NEJM and The Lancet

A KNEE-JERKER DURING PANDEMIC?

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The absence of an effective treatment against the coronavirus infection has led clinicians to redirect drugs that are known to be effective for other medical conditions to the treatment of COVID-19. Key among these repurposed therapeutic agents are the antimalarial drug chloroquine (CQ) and its analogue hydroxychloroquine (HCQ), which is used for the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.

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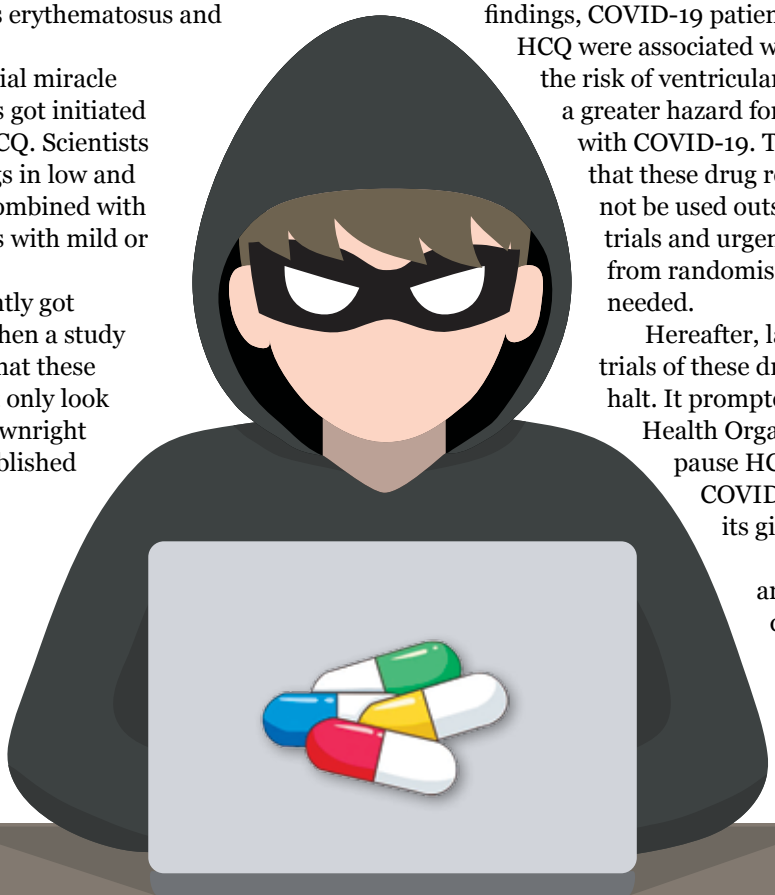
But this hope recently got struck by a big blow when a study came along claiming that these antimalarial drugs not only look in effective, but are downright deadly. This study, published on May 22 in the elite journal The Lancet, was conducted by three researchers- Dr Mandeep R Mehra from Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, US; Frank Ruschitzka fromUniversity Heart Center, University Hospital Zurich, Switzerland; and Dr Amit N Patel from Department of Biomedical Engineering, University of Utah, Salt Lake City, US.

They used hospital records procured by an American healthcare analytics company Surgisphere Corporation, established in 2008 by an Indian Sapan Desai, for their study. According to their findings, COVID-19 patients taking CQ or HCQ were associated with an increase in the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19. The study concluded that these drug regimens should not be used outside of clinical trials and urgent confirmation from randomised clinical trials is needed.

Hereafter, large randomized trials of these drugs came to a halt. It prompted even the World Health Organization (WHO) to pause HCQ clinical trials in COVID-19 patients under its giant solidarity trial.

And then came another blow when questions were raised on the authenticity of this study. For example, the claim



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President, Indian Society Clinical Research, India

"The lost precious time studying potential of the drug will be hurtful, considering that in many regions, the disease has already peaked and is now declining. Trial sponsors will find it more difficult to also convince patients to participate in the studies."

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that 96032 hospitalised patients from 671 hospitals diagnosed with COVID-19 between December 20, 2019, and April 14, 2020 met the inclusion criteria for this study, seemed implausible. Gradually, the study came under the scanner within the research community. An open letter was signed by clinicians, medical researchers, statisticians, and ethicists from across the world and sent to The Lancet.

"While we all are working at a record speed which is the need of the hour, it is of paramount importance for all researchers to ensure that the principles of ethics are followed to the core. The clinical study design, conduct, analysis and reporting should follow well-laid standards which will ensure the integrity and credibility of the data generated in addition to the following of ethical principles. Protecting patients' safety is always of utmost importance in any clinical study that we conduct. This is something that we have been doing and hence, should continue doing it in the present times too", shares Dr Chirag Trivedi, President, Indian Society Clinical Research, India.

After several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation, the authors of the paper apparently launched an independent third-party peer review of Surgisphere with the consent of Sapan Desai to evaluate the origination of the database elements, to confirm the completeness of the database, and to replicate the analyses presented in the paper.

More eyebrows were raised when the authors informed that Surgisphere would not transfer the full dataset, client contracts, and the full ISO audit report to their servers for analysis as such transfer would violate client agreements and confidentiality requirements. Eventually, the authors retracted their paper from the journal on June 5.

"The publication shifted global focus from the humble HCQ to other promising candidates, in the lead being Gilead's remdesivir. With remdesivir expected to be priced between $2,000 and $5,000 per course, pursuing HCQ could have potentially made treatment accessible globally, sooner. The publications doomed to retract led many regulatory agencies to ask scientists to halt their trials evaluating HCQ. The retraction will push safety committees to relook at those studies. No doubt, there has been time lost which could have been used to accelerate treatment for patients, especially in critical care. The lost precious time studying potential of the drug will be hurtful, considering that in many regions, the disease has already peaked and is now declining. Trial sponsors will find it more difficult to also convince patients to participate in the studies", says Megha Joshi, Consultant, Healthcare, Markets & Technology, India.

Around the same time, on June 4, Dr Mandeep

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- Dr Shree Divyya,
Manager Healthcare Advisory,
Sathguru Management Consultants, India

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- Dr Asha Bowen,
Clinician scientist, Perth Children's Hospital, Australia

"The trial has now moved on to try and urgently establish any benefits from other treatments, including antibiotics, anti-inflammatories, drugs used to treat HIV, and plasma therapies."

- Frank Hester,
Chief Executive Officer, The Phoenix Partnership, UK

"We have clearly advised that HCQ should be taken with food, not on empty stomach. We have expanded use of HCQ to frontline workers also, considering the potential benefits."

- Prof Balram Bhargava,
Director General, Indian Council of Medical Research, India

R Mehra and Dr Amit N Patel along with their co-authors Dr SreyRam Kuy from Baylor College of Medicine, Texas, US and Dr Timothy D. Henry, from Christ Hospital, Ohio, US and Sapan Desai from Surgisphere Corporation announced another paper retraction from the New England Journal of Medicine (NEJM). This study titled 'Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19', had claimed that underlying cardiovascular disease is associated with an increased risk of in-hospital death among Covid-19 patients.

"The recent high profile retraction of two controversial papers on COVID-19 by The Lancet and the New England Journal of Medicine raises several pertinent issues in the field of big data in medical research, and the fine balance of speed versus maintenance of rigorous scientific review during outbreaks and pandemics. It would seem there was indeed deliberate fabrication and fraud committed by Surgisphere, a small Chicago-based company that purportedly was able to collect and analyse tens of thousands of patient records from hundreds of hospitals in the midst of a pandemic. It is thus timely to revisit the ethical issues regarding the use of big, 'real-world data' (RWD) in order to derive 'real world evidence' to guide clinical care, healthcare policy decision making, and health service design, among other considerations. How can RWD be safeguarded against personal gain, vested interests, commercial or political influences?" mentions Dr Marcus ONG Eng Hock, Professor & Director, Health Services and Systems Research Signature Research Programme, Duke-NUS Medical School, Singapore.

An element of irony was later revealed by few media reports that meanwhile Desai, who according to court records has three outstanding medical malpractice suits against him, has written extensively in the past on research misconduct. There were further claims that major institutions including Stanford University, which were described as research partners on the Surgisphere website, said they were not aware of any formal relationship with the company.

"While the research community is always in a haste for publishing their research it is critical that they maintain integrity on the data being published. Journals rely on the declaration signed by the authors on data reliability and any conflict of interests stated. This current system has been unsuccessful in providing the required reliance on data when it is most critical with the current pandemic caused by COVID-19. Hence it could be beneficial for additional checks and balances to be created to reduce such incidences. Additionally, changes in policies of funding agencies to ensure data from research funded by these bodies to be made publicly available

will enhance transparency of research. Creating awareness on any such deterrents established by journals and data disclosure requirements by the funding agencies can increase the liability on the authors for data integrity, motivate additional prudence on authors and enhance practices for bioethics in the scientific community", says Dr Shree Divyya, Manager Healthcare Advisory, Sathguru Management Consultants, India.

Parallel to this episode came another announcement from the UK on June 4, that no clinical benefit from use of HCQ has been observed in hospitalised patients with COVID-19. In March 2020, RECOVERY (Randomised Evaluation of covid-19 therapy) was established as a randomised clinical trial to test a range of potential drugs for COVID-19, including HCQ. The trial had proceeded at unprecedented speed, enrolling over 11,000 patients from 175 National Health Service hospitals in the UK.

On this note, Frank Hester, Chief Executive Officer, The Phoenix Partnership, UK shares, "This is an important result for patient care. It was a well-powered, well-run study, with a conclusive result. The trial has now moved on to try and urgently establish any benefits from other treatments, including antibiotics, anti-inflammatories, drugs used to treat HIV, and plasma therapies."

On a positive side, low-cost drug dexamethasone showed reduction in death by up to one third in hospitalised patients with severe respiratory complications of COVID-19 in this study. Dexamethasone is a steroid that has been used since the 1960s to reduce inflammation in a range of conditions, including inflammatory disorders and certain cancers.

"The world was shocked when two of the most renowned medical journals retracted an article on COVID-19 studies. This doesn't come as a surprise because the publishing system goes through a flawed peer-review process. The lack of transparency in the selection process of the peer-reviewers reduces the accountability towards the articles published. Moreover, reviewers often try to block the competitors, steal ideas, favor authors from prominent institutions and hardly prevent bad studies from being published. That said, the more important question is, 'Why is the world obsessed over HCQ?' The recent controlled studies, one from the University of Minnesota and from the UK trial, show conclusive evidence of lack of HCQ's clinical benefit against COVID-19, neither for hospitalized patients or early exposed patients. Therefore, it is time to focus the efforts and resources to dozens of other novel and promising therapies that are being developed with controlled and well-designed studies", says Dr Neel Fofaria, Partner, MP Advisors, India.

"While additional clinical trials continue to evaluate the potential benefit of these drugs in treating or preventing COVID-19, we determined the emergency use authorization was no longer appropriate. This action was taken following a rigorous assessment by scientists in our Center for Drug Evaluation and Research."

- Dr Patrizia Cavazzoni,
Acting Director, FDA's Center for Drug Evaluation, US

"Scientific rigor should not and cannot be sacrificed for speed, as clinicians, policy makers and the general public rely on evidence based literature for informed decisions. Lives may depend on this."

- Dr Jenny Low Guek Hong,
Associate Professor, Emerging Infectious Diseases Signature Research Programme, Duke-NUS Medical School, Singapore

Following these developments, on June 15, U.S. Food and Drug Administration (FDA)revoked the Emergency Use Authorization (EUA) for CQ and HCQ. "While additional clinical trials continue to evaluate the potential benefit of these drugs in treating or preventing COVID-19, we determined the emergency use authorization was no longer appropriate. This action was taken following a rigorous assessment by scientists in our Center for Drug Evaluation and Research," says Dr Patrizia Cavazzoni, Acting Director, FDA's Center for Drug Evaluation, US.

After generating initial thoughts on resuming the HCQ trial around June 4, the final verdict from WHO came on June 17 that the HCQ arm of the solidarity trial to find an effective COVID-19 treatment has been stopped. Investigators will not randomize further patients to HCQ in the Solidarity trial but patients who have already started the medication and have not yet finished their course in the trial may complete their course or stop at the discretion of the supervising physician.

"It is timely to revisit the ethical issues regarding the use of big, 'real-world data' (RWD) in order to derive 'real world evidence' to guide clinical care, healthcare policy decision making, and health service design, among other considerations. How can RWD be safeguarded against personal gain, vested interests, commercial or political influences?"

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On June 20, Switzerland headquartered pharmaceutical company Novartis informed that it is stopping its trial of HCQ against COVID-19 due to shortage of participants. The company had initially inked an agreement with the USFDA to proceed with a Phase III clinical trial with approximately 440 patients to evaluate the use of HCQ.

The results of The Lancet study also made the researchers in Australia re-think about the AustralaSian COVID-19 trial (ASCOT) initiated by the Royal Melbourne Hospital. The trial is designed to assess the safety and effectiveness of lopinavir/ritonavir and HCQ at more than 70 hospitals across Australia and 11 hospitals in New Zealand.

"Results of a large database published in The Lancet showing an increased mortality were cause for thought, discussion and convening of a host of meetings to consider how to progress a clinical trial with emerging evidence. Here with the ASCOT trial we did all of this: convened the Trial Steering Committee, the Data Safety and Monitoring Board, the ASCOT Advisory Committee, and ultimately discussed the ongoing equipoise with the Human Research Ethics Committee. The Trial Steering Committeehas decided that ASCOT should continue recruitment and randomising patients to hydroxychloroquine containing arms", reveals Dr Asha Bowen, Clinician scientist, Perth Children's Hospital, Australia.

On the other hand, in Singapore, both the National Centre for Infectious Diseases and National University Hospital have largely stopped using HCQ to treat COVID-19 patients. "More than 20,000 articles on COVID-19 can be found on any given PubMed search since the start of the pandemic, highlighting the unprecedented speed of scientific review and turnaround. With the pandemic moving at an extraordinary pace, there is an urgent need for accurate and timely scientific evidence. Yet, scientific rigor should not and cannot be sacrificed for speed, as clinicians, policy makers and the general public rely on evidence based literature for informed decisions. Lives may depend on this", points out Dr Jenny Low Guek Hong, Associate Professor, Emerging Infectious Diseases Signature Research Programme, Duke-NUS Medical School, Singapore.

Amidst this confusion, another announcement came from the Taiwan Food and Drug administration on June 17 in the form of recalling 11 medicines containing a compound called fenspiride, used in the treatment of certain respiratory diseases. In a statement announcing the recall, the FDA cited the suspension of fenspiride medicines by the European Union (EU) in 2019, which warned that such medicines could cause sudden serious heart rhythm problems. This development has once again highlighted the damaging effects caused by certain drugs being used for treating respiratory disorders.

But for India, the speculations over the effectiveness of HCQ was never a cause of concern, even when the negative study was published. On May 26, Prof Balram Bhargava, Director General, Indian Council of Medical Research stated, "We have clearly advised that HCQ should be taken with food, not on empty stomach. We have also emphasized that one ECG should be done during the treatment. We have expanded use of HCQ to frontline workers also, considering the potential benefits."

As a matter of fact, Dr Shekhar Mande, Director-General, Council of Scientific and Industrial Research in India had called WHO's initial stay on HCQ trials as a knee-jerk reaction. Any which way, the studies on HCQ should finish and answer the questions they were designed for. So that we won't have to revisit this particular question again and we can look at new options. BS

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