Open Letter to: Mayla Gabriela Silva Borba, MD; Fernando Fonseca Almeida Val, PhD; Vanderson Souza Sampaio, PhD; Marcia Almeida Araújo Alexandre, MD; Gisely Cardoso Melo, PhD; Marcelo Brito, MSc; Maria Paula Gomes Mourão, MD; José Diego Brito-Sousa, MSc; Djane Baia-da-Silva, PhD; Marcus Vinitius Farias Guerra, MD; Ludhmila Abrahão Hajjar, MD; Rosemary Costa Pinto, BSc; Antonio Alcirley Silva Balieiro, MSc; Antônio Guilherme Fonseca Pacheco, MD; James Dean Oliveira Santos Jr, PhD; Felipe Gomes Naveca, PhD; Mariana Simão Xavier, MSc; André Machado Siqueira, MD; Alexandre Schwarzbold, MD; Júlio Croda, MD; Maurício Lacerda Nogueira, MD; Gustavo Adolfo Sierra Romero, MD; Quique Bassat, MD; Cor Jesus Fontes, MD; Bernardino Cláudio Albuquerque, MD; Cláudio-Tadeu Daniel-Ribeiro, MD; Wuelton Marcelo Monteiro, PhD; Marcus Vinícius Guimarães Lacerda, MD

Authors of: Effect of High vs. Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection A Randomized Clinical Trial. JAMA April 24, 2020

And to:
Howard Bauchner, MD, Editor in Chief, JAMA
Richard Horton, Editor in Chief, The Lancet
Jeffrey Drazen, MD, Editor in Chief, NEJM

The signatories to this letter raise multiple concerns regarding the methodology, dosages, and randomization in this study.

This clinical trial of hospitalized patients with SARS-CoV-2 infection took place from March 23-April 5, 2020 in the largest public hospital caring for Covid-19 patients in Brazil. Patients in the study received either "high-dose" or "low-dose" chloroquine as the intervention. The published result was that high-dose chloroquine should not be used in patients with severe Covid-19 disease.

In response to this and similar findings in other scientific journals which stated that CQ or HCQ was either ineffective or risky, the World Health Organization ordered nations to stop using HCQ and CQ, WHO Chief Tedros suspended trials being held in hundreds of hospitals across the world, EU governments France, Italy, and Belgium banned HCQ for Covid-19 trials, and there was worldwide ridicule heaped upon the United States. All the negative journal studies and press attention has made it extremely difficult to enroll patients in hydroxychloroquine studies. Even now, in the very large RECOVERY trial, hydroxychloroquine is being called ineffective, even though that study suffers from many of the same problems that are seen in the JAMA study. The lead RECOVERY author has taken the unusual step of dramatically informing a worldwide audience not to take hydroxychloroquine even prior to publication.

Due to the unprecedented animosity toward a medication with: a superb safety record for 65 years; preliminary data that it was helpful; a mechanism of action that supports the scientific theory that the medication would be efficacious; substantial and growing anecdotal evidence that it is indeed effective; and a growing pile of infamous studies that have earned a place in the garbage heap; the undersigned took a close look at the JAMA study published on April 24, 2020 that also claimed CQ was not only ineffective, but dangerous. At this overdue date, we have three demands.

First, we demand an immediate retraction of the JAMA study by Borba et al., similar to the retractions of the negative HCQ studies published in The Lancet and NEJM.

Second, we demand a halt to the publication of any studies of HCQ/CQ that use supra-toxic dosages.

Third, we demand a formal joint statement of explanation from the Editors of JAMA, The Lancet and the NEJM regarding how/why they, ostensibly independently, virtually simultaneously accepted and then published such obviously compromised studies.

We will start with the scientific compromise of the study itself, followed by JAMA's role in perpetuating misinformation, followed by the three journals joint culpability in the failure of the scientific process.

I. Scientific Compromise of the JAMA Study Itself

1. Pseudo-randomization of patients. The authors assert that the patients in the study were randomized to be in one of two groups, either a "high-dose" or "low-dose" chloroquine group. However it is clear that the groups were not randomized but were very imbalanced in terms of underlying risk of developing more severe disease. The risk factors for becoming very ill with Covid-19 are well established and include certain clinical features such as: older age, diabetes, heart disease, hypertension, kidney disease, AIDS. Being more ill at the time of presentation as evidenced by higher fever, organ failure. Virtually all of the patients with the higher risk factors were assigned to the "high-dose" group. We estimate the probability of that happening randomly to be 2%.

2. No evidence of an ethics board oversight. All research involving human studies must be conducted under the auspices of an ethics board. The World Medical Association Declaration of Helsinski – Ethical Principles for Medical Research Involving Human Subjects states: "the research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. The authors, in the preliminary *medRxiv* version of the manuscript, state that an Ethics Committee approved and that the *Conselho Nacional de Ética em Pesquisa* (CONEP) authorized the study under the number 3.929.646/2020. However such approval was absent from CONEP's *Plataforma Brasil* site where all information on projects submitted to ethical scrutiny is available. Note that no information on the CONEP approval number is present on the JAMA article. There was no CONEP approval prior to publication and for at least six weeks post-publication.

3. Supra-toxic dosages of chloroquine were used. More than 30 years ago the lethal dose of CQ was established to be 5 grams, and 4 grams is linked to very severe neurological and cardiovascular toxicity. Because CQ stays in a person's body for a very long time, with a half-life of 30 days but as long as 60 days in very ill patients, doctors are cautious about the total amount used. The elderly, hospitalized, very ill patients assigned to the high-dose group received 4.8 grams in just four days and 12 grams if they survived to the full ten days. Unsurprisingly so many people died in the high-dose group that the high-dose group had to be halted.

II. JAMA's Role in Perpetuating Misinformation

1. JAMA knew prior to publication that this study was both irredeemably flawed and of insufficient quality to be published in a premier medical journal.

   a. the authors administered a known lethal amount of a medication

   b. the patients were not randomized

   c. there was no ethics board oversight

2. JAMA Editor in Chief Mr. Horton was alerted post publication about these problems by scientists who requested that JAMA retract the study. JAMA denied this request even while knowing that Brazil had started a civil investigation into the scientists who authored the study.
3. The dosage of CQ in the JAMA study was so high, that Brazil is continuing its civil investigation but now has also opened a criminal investigation. JAMA still has not retracted this study.

III. The three most famous medical journals in the world have jointly and erroneously condemned HCQ/CQ.

This JAMA study joins the editors of The Lancet and the NEJM studies in particularly lacking in ethics and integrity. We believe the problem is the current editors of these prestigious journals not the journals that have a longstanding reputation of excellence. Together these three journals are arguably considered the three most famous medical journals in the world, and as such, together they bear particular responsibility for their joint claims. Thus together they must correct their mistakes.

The compromise of the scientific process has caused the following harms.
1. likely contributed to the death or worsening illness of at least hundreds of thousands of patients worldwide
2. diminished the public confidence in scientific journals
3. harmed the reputation of all scientists

It is unknown to us how this terrible compromise of scientific integrity has come to pass. But when the three leading medical journals in the world, all ostensibly acting independently, accepted for publication, and then actually published, studies with such shockingly terrible data, methodologies, and processes, virtually simultaneously, it gives the appearance of wanting to arrive at a pre-determined conclusion, which is contrary to all science and anathema to scientists.

Many theories could be postulated as to how this has come to be, and we offer one.

Dr. Dousty-Blazy, the former French Health Minister, Under Secretary General of UN, and candidate for Director of WHO has publicly stated that The Lancet and the NEJM Editors admit to being pressured by pharmaceutical companies to publish certain results.

> "The Lancet's boss … said … the pharmaceutical companies are so financially powerful today and are able to use such methodologies as to have us accept papers which … in reality manage to conclude what they want ... I have been doing research for 20 years of my life. I never thought the boss of The Lancet could say that. And the boss of the NEJM too. He even said it was "criminal."

Even as we write this letter we are gravely concerned about studies currently in progress that are similar to the JAMA study in using supra-toxic dosages of medication. We are concerned not just for the immediate safety and well-being of the specific patients enrolled in these studies worldwide, but because such studies seem to be focused on reaching a pre-determined conclusion that HCQ/CQ is at best ineffective and at worse, harmful.

The RECOVERY trial is particularly problematic because it is so large and considered to be particularly authoritative. Unfortunately, patients are receiving 2.4 grams of HCQ in the first 24 hours and 800 mg. daily thereafter. That is 4.8 grams at the end of the fourth day, which is toxic. Within the RECOVERY paper itself the authors acknowledge that they are using twice the normal dose. Not only should a study with such toxic dosages immediately be halted, no scientific conclusion can be permitted to be drawn from such dosages, and no credibility can be attached to such data.

Despite the obvious problem attendant to giving supra-toxic dosages, the lead author of the RECOVERY trial, Dr. Martin Landray, has already publicly stated the medication is the problem, not the *amount* of the medication: "If you, your spouse, your mother get admitted to hospital and is offered hydroxychloroquine, don't take it."

Knowing the dosage is supra-toxic, and hearing the lead author publicly state that HCQ is not to be used even *prior* to publication, we think it is critical that the leading medical journals commit to refuse to publish data from studies that use too much of a medication.

This seems like such an obvious request that it is difficult to believe we must even request this! Not only is using supra-toxic dosages poor science, but it strongly suggests a pre-determined conclusion. No honest journal editor should risk their reputation by publishing studies in which it is impossible to know if patients died by overdose when in reality, they could have been helped by a proper dosage.

Like the JAMA study, and The Lancet study and the NEJM study before that, studies from RECOVERY have no scientific credibility because of poor study design from inception. If studies based upon poor design continue to be published, they will inevitably continue to be retracted post-publication, but in the meantime, irreparable harm to real patients will continue to accrue and the public's faith in science will continue to deteriorate.

In summary, we make the following demands.

1. We demand JAMA retract the article by Borba et al., published April 24, 2020.

2. We call on JAMA, The Lancet, and NEJM to refuse to publish flawed studies specifically those using supra-toxic dosages of HCQ.

3. We call on JAMA, The Lancet, and NEJM to jointly explain what internal or external pressures caused or contributed to the scientific process becoming so polluted, and to present a specific plan to ensure this cannot happen again.

Signatories:

Simone Gold, MD, JD, FABEM