Selection bias trap

(On Covid-19 and Hydroxychloroquine *The Lancet* - SCANDAL)

Dragan Pavlovic

The Harvard Medical School produced 3 important papers this spring. The first 2 are certainly the EVENT worth discussing. As David Hume would probably write :

"If we take in our hand any volume; of divinity or school metaphysics, for instance; let us ask, Does it contain any abstract reasoning concerning quantity or number? No. Does it contain any experimental reasoning concerning matter of fact and existence? No. Commit it then to the flames: for it can contain nothing but sophistry and illusion."

> *David Hume, An Enquiry Concerning Human Understanding* (1748) sect. 12, pt. 3

The articles, besides of probable absence of the facts and truths, contained methodological mistakes of the first order. Yet, our reality is that it is the normal research that concerns Hydroxchloroquine therapy which is in the focus of all media that try, in wain though, to "demonstarte" its inefficacy in Covid-19 pandemic! How strange. Since the real scandal, no doubt is those Harvard papers, that were, methodologically, a **real disaster. Yet they were published in the most valued worldly medical journals! A scandal** not matched in the history of modern science. Look the timeline: While the Professor Raoult paper that initiated the debate, was a simple report on the use of a possible drug for Covid-19 urgently needed therapy, probably Evidence Medicine Level 3d, *The Lancet* and *NEJM* papers are an extreme scientific failure combined with a major public scandal. It is not easy to believe that (1) the Harvard scientists would, "by mistake" conceive such a study, (2) that the two most prominent medical journals would "by mistake" accept to publish such papers, that (3) the World Health organisation (WHO), (4) the French government and (5) the French Scientific counsel would just "by mistake" one day after the publication of The Lancet paper, ban the HCQ!

The real scandal of the Covid - 19 pandemic are Harvard papers published in The Lancet and the NEJM, and not the marseille Professor Raoult paper. There is certainly clear logic behind. To destroy Donald Trump, who believes that HCQ works? I do not know. Any conspiracy theory will do for the moment, including human stupidity.

Which Harvard papers I have in mind? I will first give a list and then discuss just the first paper published in *The Lancet.* The paper of Didier Raoult, that somehow initiated the debate, I will just cite in the commentary submitted to *The Lancet*. So here are they:

1. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis, Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31180-6.pdf
Unbelievable Fraud. RETRACTED June 5, 2020:
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31324-6/fulltext

2. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19
List of authors. May 1, 2020,
Mandeep R. Mehra, M.D., Sapan S. Desai, M.D., Ph.D., SreyRam Kuy, M.D., M.H.S., Timothy D. Henry, M.D., and Amit N. Patel, M.D. https://www.nejm.org/doi/full/10.1056/NEJMoa2007621
Unbelievable Fraud by the same authors. RETRACTED June 5, 2020
https://www.nejm.org/doi/full/10.1056/NEJMc2021225?medium=organic-social&source=nejmtwitter

3. The last is then:

Analysis of hospital traffic and search engine data in Wuhan China indicates early disease activity in the Fall of 2019

https://dash.harvard.edu/handle/1/42669767

https://www.nejm.org/doi/full/10.1056/NEJMoa2007621?query=recirc_curatedRelated_article

Citation Nsoesie, Elaine Okanyene, Benjamin Rader, Yiyao L. Barnoon, Lauren Goodwin, and John S. Brownstein. Analysis of hospital traffic and search engine data in Wuhan China indicates early disease activity in the Fall of 2019 (2020).

Original Résumé. The global COVID-19 pandemic was originally linked to a zoonotic spillover event in Wuhan's Huanan Seafood Market in November or December of 2019. However, recent evidence suggests that the virus may have already been circulating at the time of the outbreak. Here we use previously validated data streams - satellite imagery of hospital parking lots and Baidu search queries of disease related terms - to investigate this possibility. We observe an upward trend in hospital traffic and search volume beginning in late Summer and early Fall 2019. While queries of the respiratory symptom "cough" show seasonal fluctuations coinciding with yearly influenza seasons, "diarrhea" is a more COVID-19 specific symptom and only shows an association with the current epidemic. The increase of both signals precede the documented start of the COVID-19 pandemic in December, highlighting the value of novel digital sources for surveillance of emerging pathogens
NOT YET RETRACTED.

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Below is our Commentary on the first *The Lancet* paper by Mehra et al. (3), submitted on 23the May 2020. We are waiting for the response to the second appeal. We, of course, claim no knowledge about the efficacy of the HCQ and do not discuss the agent at all.

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The Lancet Covid-19 Therapy Study: another miss-out

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The work by Mehra et al. (3) is an interesting analysis of a multinational registry. However, the reader should be reminded that this analysis is based on retrospective, historical, a type of

clinical studies that have been known for years to contain all possible errors that such not randomized approach research may have. It looks exactly like the analyses that were often praxis in the 50es and 60es of the past century, unfortunately, produced many unreliable results. Particularly if they were multicentre studies and very large. Exactly as this study is. The problems with such studies are abundant and it will be impossible to list even the most important. We discuss here *The Lancet* paper methodology. The paper maintained, for example, that since non-survivals had more often HCQ then survivals - HCQ killed people. An example with oxygen may be sufficient to some. Indeed, oxygen. which the non-survivals had more often - why the conclusion cannot be that oxygen killed some COVID-19 patients? This would certainly be confusing risk factors with causal factors. being a man, obese, being in the ICU, would be the risk factors but not causal factors. Suffering from COPD may adjacent causal factor for a lethal outcome, so adjacent causes. Here below is **just a trivial fraction** of the methodological objection. The serious legal questions are being discussed by several other commentators and we will not go into them.

For example, how do we know that the control groups were comparable to the treatment groups? In such a study it is very hard to retrospectively fulfil the demands for fair randomisation. If more patients at risk were in the group that receiving chloroquine and the healthier, not at-risk patients, were in the control group, then the outcome would be heavily biased. The tables show that the patients were similar, but do not show the degree of risks, that could be very different to start with. One COPD is not the same as any other COPD. As looked at from the outcome side, the non-survivals had much more often comorbidities than survivals (Table 1), which implies a selection bias.

This is a retrospective study. So let us look at the study how it would look from the start to the intervening physician. If we assume normal behaviour of the physicians or just see how this was in France when the government and the Scientific commission finally accepted to encourage clinical studies: and quite logically: the hydroxychloroquine (HCQ) had to be administered only in hospitals and just to the patients at risk and with more advanced serious symptoms; in fact on March 24, 2020, it was permitted to be given ONLY to the patients with grave symptoms! (4). The atmosphere in France was against HCQ and the use only in the patients with high risk (of dying) was encouraged - the agent was requisitioned by the governmental order already in January for these purposes. The drug was not prescribed

without bias already from January 2020. The situation in the world was probably also influenced by this "Zeitgeist".

The Mehra et al. study (3) included 50 European hospitals, but the real question is: from which hospitals and how many patients from France for example? A large number of Covid-19 patients were included in France into the "Discovery" studies which included over 800 hospitals only in France and should have included 3200 hospitals in the world! These studies examined the mentioned agents ONLY in patients at risk or gravely ill. If hydroxychloroquine was given more to patients that had more chances to die (what the regulation from 24. march, 2020 imposed !) then those that did not receive it, a *selection bias* was more then obvious. Besides, not to state how the hospitals and countries were chosen is a grave problem, since the number of hospitals was large and the criteria of choice must be communicated and the method about how the bias was avoided is necessary to disclose.

Also, the decision to administer or not the chloroquine or hydroxychloroquine to the patients presented with the Corona-19 symptoms (in the hospitals all over the world - France included) was most probably spontaneously guided by the known risk factors that the patients presented (not just presence but the degree of obesity, diabetes, age, chronic respiratory affections), i.e. in France for sure, but also elsewhere, the patients at risk were **more likely** to receive chloroquine or hydroxychloroquine. The percents for those data on table 2 show exactly this, that the patients at risk received that therapy more often. Let us examine now how this looks like from the present time, retrospectively. No wonder, then, that we find, when we look retrospectively, that more non-survivals received the mentioned therapy. But this does not establish the causal relationship between administration and death of the patients, as the authors propose. On the contrary, it shows that the differences in the frequency of the chloroquine and hydroxychloroquine administration between the two groups, survivals and non-survivals group, examined retrospectively, the finding that non-survivals have had the mentioned agent as therapy, was no doubt, due to conscious, intelligent human intervention, a coherent behaviour of the caring physicians or because the French physicians were obliged to administer the agent only to the patients that had a higher risk of dying. A large such study that included just the grave patients was running in France from March 24, 2020 - how many of those patients were included in the Mehra et al. study? Unfortunately, some of the patients that were at risk, indeed died, despite having chloroquine

or hydroxychloroquine. Some, of course, survived, and this is good. This is all that we know for the moment.

Or why exactly all "treatment" groups were worse than "no-treatment groups"? Is this just because all treatments were "dangerous"? Who will believe this? If just the patients who were considered to need "some therapy", received chloroquine therapy, the bias was introduced in advance and this can hardly be retrospectively corrected. Also coronary artery disease, congestive heart failure, and arrhythmia patients it seems that also received Chloroquine? Those were considered to be contraindications for administrating the mentioned agents and can explain cardiac complications that were observed in the study - in the groups that received those agents. The most likely conclusion will then be that the agents produce undesirable complications if used beyond the recommendations. We do not need to elaborate more here because the error in selection is obvious. Besides, the "controls" apparently had no therapy whatsoever (those as "unimportant" are placed in the appendix), apart from ACE inhibitors, use of statins, use of angiotensin receptor blockers. Something is missing in this study.

This is again one in the series of non-randomized or in many different ways problematic studies that try to evaluate the relevance of the initial Marseille study (5). The Marseille study is apparently in the middle or upper part of low level on the Evidence-Based Medicin Level scales (6) so it is not to be rejected at this stage. This time the patients were collected from several different hospitals in the entire world (671 hospitals in six continents) where nobody can know which hospitals were taken, how the patients were chosen and treated. If in some town hospital the ICU patients received HCQ and some ordinary rural hospital patients did not, they will never be comparable. But how the authors of the analysis made their choices? What relevance will this study have? Well, the authors stated " *Even if these limitations suggest a conservative interpretation of the findings, we believe that the absence of any observed benefit could still represent a reasonable explanation."* and this is absurd. Proving that something is not the case is just a trivially empty task. A demonstration of "absence" of something has no content.

The analysis of Dr Mehra et al. is no doubt demonstrating that the examined agents probably are not of much use for the COVID-19 patients which are in the advanced phase of the

disease and that when used, the well-known contraindications should be respected. We desperately need a study that verifies the initial Marseille finding (5), a coherent randomized clinical trial with the results that will contain hard facts. And this will not be finally "a clarification" but just a start of the efforts that will aim at finding out whether HCQ may have some effects on COVID-19. Indeed, the question that remains is which randomised Clinical Trial (RCT) would be able to establish a reliable response.

The RCT do not in principle verify whether the agent by itself has some effect on a particular disease. As we tried to show (8), such studies establish only whether the particular therapy in some social settings (hospital, outpatient, or any other well-determined settings, produces some effect that are different from the effects of placebo. An ideal setting (the same time, place, identical groups, identical all confounding factors) is impossible to assure. Clinical studies than in fact establish the effects of more than tens or hundreds reasonably well or even badly controlled, but including also uncontrolled factors - together with the effects of the examined agents. The result is hard to interpret if the differences are small. If they are sometimes found they may be accidental. Often such studies are even organised in many centres where the circumstances, from recruitment until therapy are so varied that no homogeneity is never to aspire. Finally, even if one such study would establish efficacy or no efficacy of the HCQ for therapy of Covid-19, we will need a next study to confirm the results. And we are on the way to the infinite regress. When we know the history of science and medicine and are aware that probably 30% of the (results of the) studies are, after about 30 years, considered as invalid and the earlier agents often even considered as contraindicated, we must conclude that to look for some better methods is necessary. The better approach may be a clear pathophysiological method where we would lay on basic science and instead to be the slaves of statistics, to look for mechanisms of the diseases and the mechanisms of action of the agents. Somewhere in between will probably be the right solution to the right therapy question.

1. Altman, Douglas G; Bland, J Martin (1995). "Absence of evidence is not evidence of absence". British Medical Journal. 311 (19 August): 485.

2. Sagan, Carl (1997). The Demon-Haunted World: Science as a Candle in the Dark (1st ed.). New York: Ballantine. p. 213. ISBN 0-345-40946-9.

3. Mehra MR, Desai SS, Ruschitzka F, Patel AN, Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet.* 2020; (published online May 22.)
https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31180-6.pdf
(Viewed on 23rd May 2020)

4. https://www.thelocal.fr/20200324/france-allows-chloroquine-to-be-given-to-gravest-coronavirus-cases (Viewed on 23rd May 2020)

https://presse.inserm.fr/en/launch-of-a-european-clinical-trial-against-covid-19/38737/
(Viewed on 23rd May 2020)

5. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; published online March 20. DOI:10.1016/j.ijantimicag.2020.105949.

6. From the Centre for Evidence-Based Medicine, Oxford
For the most up-to-date levels of evidence, see www.cebm.net/?o=1025
Or, Stony Brok Univesity Library, Frank Melville Jr., Memorial Library, Stony Brook University, Stony Brook, NY 11794-3300.
https://guides.library.stonybrook.edu/evidence-based-medicine/levels_of_evidence
(Viewed on 23rd May 2020)

7. https://www.reuters.com/article/us-health-coronavirus-hydroxychloroquine/france-bans-hydroxychloroquine-to-treat-covid-19-idUSKBN233197?il=0 ((Viewed on 27th May 2020)

8. Dragan Pavlovic. Two problems of empirical biomedical science: example of awareness monitoring with bispectral analysis. *Eur J Anesth*, 26: 87-9, 2009.

Important French links, viewed on 23rd May 2020:
https://www.francetvinfo.fr/sante/maladie/coronavirus/agnes-buzyn-et-son-mari-didier-raoult-et-la-chloroquine-on-a-examine-au-microscope-les-20-affirmations-d-un-message-cense-prouver-un-scandale-d-etat_3891385.html

https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000041755775&categorieLien=id