

I obtained the above-cited recent study from the Internet. The article was announced also on various media and alarming news deserves to be examined more closely. Hydroxychloroquine (HCQ) is an agent that is used extensively in the world for malaria and various inflammatory conditions. Its use in COVID-19 has been controversial.

The Pradelle paper describes a quite large study, in the form of meta-analysis.

#Our reply

That is not strictly correct. We produced a model with parameters that have been estimated via meta-analyses.

It was found 16,990 HCQ-related in-hospital deaths in 44 cohorts studies.

#Our reply

That is not correct. We did not “found” a number of HCQ-related in-hospital deaths “in 44 cohorts studies”, we provided an estimate of the number of HCQ-related in-hospital deaths for the countries with available data. The systematic review and meta-analysis of the 44 cohorts provided estimates of mortality rate and of HCQ exposure that were used with other parameters (number of hospitalizations, relative HCQ effect on death).

I was very much interested in obtaining a deeper understanding of the results since I was involved in a discussion about the use of HCQ at the beginning of the pandemic, in 2020 (reference 1, see below, also for the references cited later). Unfortunately, since it is only an estimate of the potential risks from the use of the HCQ (as stated in the title) and the data are not only very large but almost not directly available being a meta-analysis, it is hard to form a more secure judgment about the given results.

#Our reply

It is unclear what “data are not only very large but almost not directly available being a meta-analysis” means.

Yet some formal reserve concerning the findings persists. The paper suffers from well-established drawbacks that retrospective studies have and also from the problems that meta-analyses have in principle. The retrospective and meta-analyses often introduce well-known selection bias to the interpretation of the effects of the agent i.e. preclude the possibility of making reliable judgments concerning the effects of an agent that is administered to the groups of patients some of which had increased risks before the agent is administered.

#Our reply

The effect of HCQ on the risk of death in COVID19 patients was estimated via the systematic review and meta-analysis of Axfors et al. (1) as explained in the methods section. This meta-analysis included randomized trials, i.e. the design that allow inferring causal treatment effect.

Those are some of the general reserves that I already expressed in my paper about the Lancet and the New England Journal of Medicine articles in 2020 that apply here. Let me trace the basic problem. The paper of Pradelle that I comment on is in a row of a very large series of papers related to COVID-19 pandemic that were rapidly written and that were based on superficial but urgent clinical studies which in addition rarely had correctly designed controls.

#Our reply

It is unclear what that means.

For example, the original paper on hydroxychloroquine (HCQ) from Marseille was obviously just a pilot study.

#Our reply

Without reference, it is unclear which study is discussed here.

Indeed, the “response” was even more problematic, since the Lancet and the New England Journal of Medicine papers were projected as very large multicentre data- analyses – to be retracted as unreliable and legally suspicious collections of data with obvious, as I maintain, selection bias concerning HCQ effects. Unfortunately, the paper of Pradelle et al. is not much different.

#Our reply

It is unclear what “response” means. Without reference, it is unclear which studies are discussed here.

This meta-analysis included studies after August 2020. when HCQ was practically forbidden in France and very seldom used in Europe.

#Our reply

See previous comment.

Then, these drawbacks combined with a general belief that existed at that time that only the patients with serious risks should have the agent preventively, or, what introduced even more serious bias – they should have it when the disease already was in the later stages (affecting in particular respiratory system), impose mortal selection bias and represent serious objections to the present study.

#Our reply

It is unclear if that refers to the evaluation of the treatment effect of HCQ in COVID-19, if that’s the case please see previous comment.

This methodological shabbiness could have been justified during the epidemic by the need to have at least some information. Nevertheless, after the critical years, we need serious studies designed with utmost care to verify many of the rapid and superficial conclusions from the time of pandemic. The commented paper is obviously based on the possibly problematic “studies”

#Our reply

It is unclear why it would be “obviously based” and what means “based on the possibly problematic “studies””.

and although being “an estimate” does not express sufficient reserves that almost certainly apply to the used studies.

#Our reply

We highlighted the limits of our estimates in the paper.

Instead of trying to reinforce probably false conclusions driven by the mentioned studies, papers are needed that would address the probably too rapid conclusions that marked almost all papers published during the time of the pandemic.

#Our reply

The link with our paper is not clear.

I understand that authors could not retrospectively consider all the risks for the patients who received HCQ therapy in so many different institutions worldwide. Neither could they take into account retrospectively timing of the administration of the HCQ, comparable risks for the patients, nor routine cardiologic contraindications as traditionally recommended. In other words, the task was a priory unattainable in principle. Much larger databases exist that clearly contradict the conclusions of the Pradelle study (2).

#Our reply

The reference to source 2 is unclear: it appears to be a blog. It's unclear whether it has undergone peer review. The link in reference 2 provides 8 references, it is unclear which one(s) would be the "Much larger databases exist that clearly contradict the conclusions of the Pradelle study".

It seems to be hosted by the website of the IHU – Méditerranée Infection institut that has promoted the use of HCQ for COVID-19 and that has been suspected of various scientific misconduct (1).

It is however regrettable that authors did not express more clear reserves towards the interpretation of the results of this study that would prevent media from misuse. Indeed the misuse in the media is already present today in France and the only that can be done now is to promptly inform the general public that the mentioned paper displays only estimates founded on very problematic and superficial data obtained by retrospective analysis of already published often controversial and not standardized results of the studies worldwide.

#Our reply

We highlighted the limits of our methodology in the paper. It is unclear what means "very problematic and superficial data" and "often controversial and not standardized results".

REFERENCE

1. Axfors C, Schmitt AM, Janiaud P, Van't Hooft J, Abd-Elsalam S, Abdo EF, et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. *Nat Commun* 2021;12:2349.
2. ['Failure at every level': How science sleuths exposed massive ethics violations at a famed French institute. Available at: https://www.science.org/content/article/failure-every-level-how-science-sleuths-exposed-massive-ethics-violations-famed-french. Accessed June 20, 2024.](https://www.science.org/content/article/failure-every-level-how-science-sleuths-exposed-massive-ethics-violations-famed-french)