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Why has France not given itself the means to show the ineffectiveness of Hydroxychloroquine in COVID-19?

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Abstract

The effectiveness of hydroxychloroquine in COVID-19 is still disputed at this time, particularly by opposing demonstration by randomized studies and observational studies. But why this difference between data from randomized and observational studies? Has France given the means to answer the question of the effectiveness of hydroxychloroquine through randomized studies?

Keywords: COVID, Hydroxychloroquine, power, sample size, false negative studies

To the Editor,

We read with interest the paper by Ader et al. [1] reporting the absence of efficacy of Lopinavir/Ritonavir (L/R), L/R-IFN- β -1a, and hydroxychloroquine (HCQ) in the French DisCoVeRy trial. In this article the sample size calculation was estimated to be 620 patients by arm to achieve a study power ($1-\beta$) of 90% and a two-sided Type 1 error (α) of 5%. Their conclusion was that in hospitalized adults with COVID-19 none of the experimental drugs tested improved the clinical status at day 15. As reported in their table 2, the overall number of patients included is 583; 148 as control, 145 in L/R, 145 in L/R/IFN, and 145 in HCQ indicating that the study is severely underpowered. In the same table, death is reported on day 15 in 6/54 (11%) of severe cases in the control and in 3/52 (5.8%) of the severe cases in the HCQ arm. At this stage, the Type II error (β) is 63.3%, which means that the authors have more than a 50% chance of being wrong when they state that there is no benefit of treatment in this population. This is confirmed on day 29 ($\beta = 85.2\%$). Similarly, in another French trial multicentric RCT, HYCOVID [2], a placebo-controlled double-blind trial, and theoretically the gold standard from a methodological point of view, the mortality on day 28 between HCQ and the Placebo was reported to be 6/124 (4.8%), and 11/123 (8.9%),

relative risk 0.54 (0.21-1.42) which, while not significant, reduce the risk of death by half. Here, the Type II error (β) was 75.3%. Accordingly, the probability of falsely concluding that there was no difference was extremely high. Considering these two severely underpowered studies ($1-\beta$ of 15 and 25%, respectively), we wondered whether French studies were given the means to show the ineffectiveness of HCQ for COVID-19 mortality.

In this context, we calculated whether the trials and observational studies carried out in France had the number of participants and therefore the power necessary to detect a reduction in the risk of mortality by a factor of two (-50%) with treatment (confidence level 95%, power 80%). The higher the fatality rate among untreated patients, the smaller the number of patients needed (Figure 1A). In practice, none of the trials carried out in France on HCQ outside our center recruited enough patients to reach the power to detect a 50% reduction in the risk of mortality (Figure 1B). In our center, Lagier et al., 2021 [3] had a very high power (90% of the necessary number of patients) whereas Million et al., 2021 [4] had a power level slightly lower than the theoretical number of patients to find a 50% difference in the risk of death. However, as a decrease in mortality risk of more than

50% was found (-83% in patients older than 60 years, no deaths before 60 years), the difference was significant and these studies were not underpowered.

Since March 2020, we have proposed HCQ-azithromycin (HCQ-AZ) dual therapy. In HYCOVID [2], we were interested to see that the authors mention, only in the supplementary data, that none of the patients who had HCQ-AZ at randomization had the primary outcome (death or transfer to intensive care unit at Day 14) compared with 3 out of 11 in the placebo group. The situation is the same in Mahevas et al., 2020 [5] where 0 out of 15 patients with dual therapy died, but no statistical test is proposed, and this is not even discussed. These two studies did not test the value of dual therapy and did not report this interesting result in their conclusions. Apart from our center, no French study has tested HCQ-AZ with enough patients to demonstrate a possible difference of HCQ-AZ on mortality. In the meta-analysis provided here, we were able to show that the French studies, although heterogeneous, identified a beneficial and significant effect of HCQ-AZ on mortality with a 63% reduction in the risk of death. The effect of HCQ alone showed a 20% non-significant decrease in the risk of death (Figure 1C & 1D).

Finally, if the objectives were to demonstrate that outcome was not different with HCQ compared to standard of care or placebo, the underpowered studies above do not allow to draw any conclusion. The enrolment was stopped too early, and this after the Lancet gate and the announcement of WHO on May 25th to suspend then stop trials with HCQ. Was it an opportunity? Why did France not finish their studies to reject the null hypothesis to be able to conclude? Never mind, among French studies, observatory studies can clearly state that HCQ especially when associated to azithromycin reduces risk of death in COVID-19, but RCT, unfortunately, did not allowed to state that this is not true.

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Conflict of interest

All authors are not in conflict of interest with the content of this manuscript.

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Figure A. Sample size needed to test a 50% mortality risk difference according to infection fatality rate in untreated ($\alpha = 5\%$, $\beta = 80\%$), **Figure B.** Percentage of the real sample size on the theoretical sample size needed to test a 50% mortality risk difference.

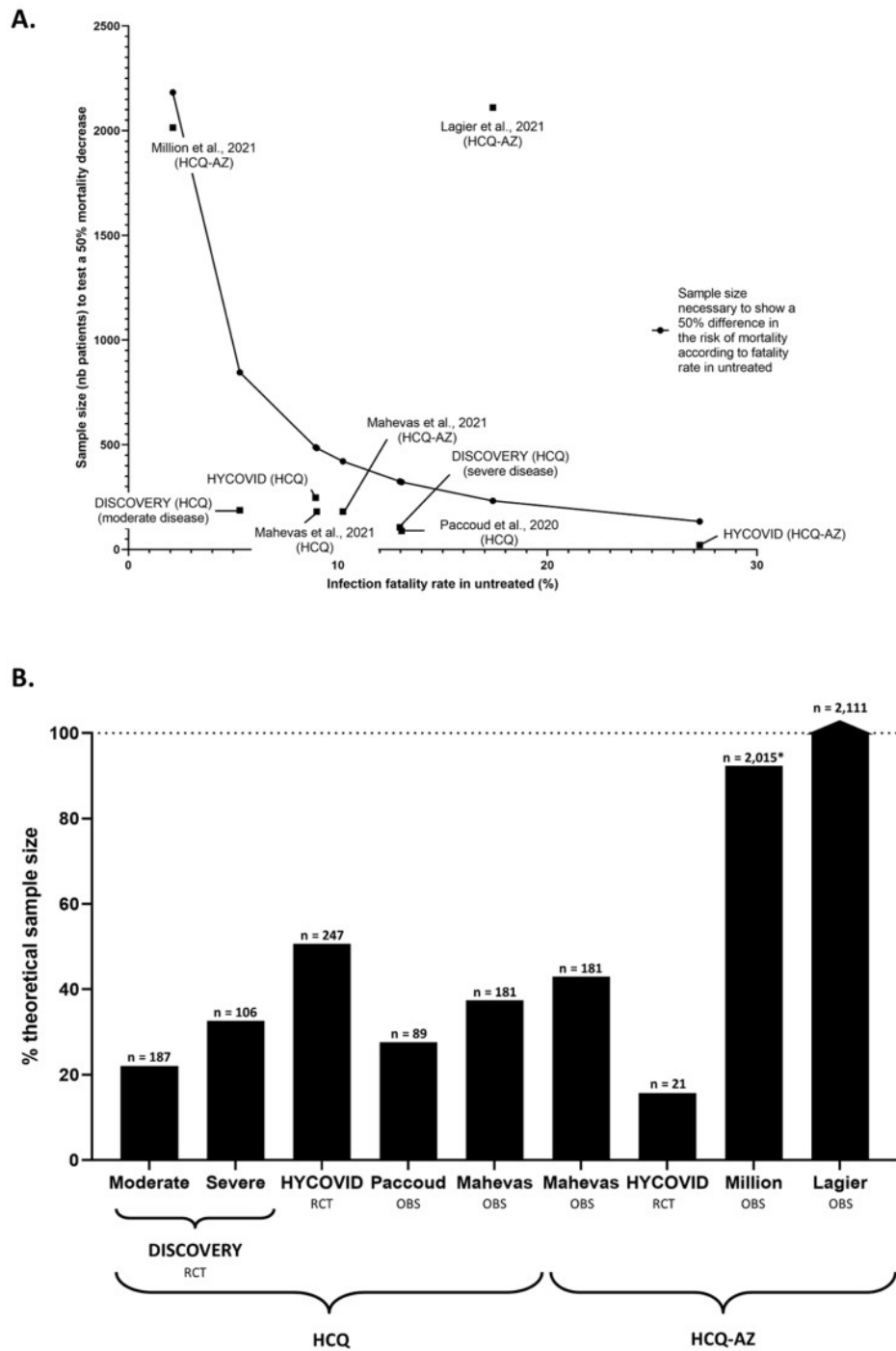
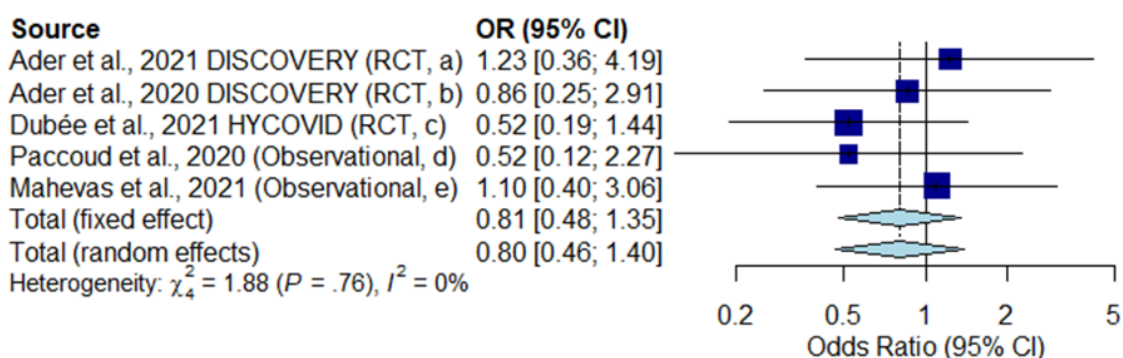
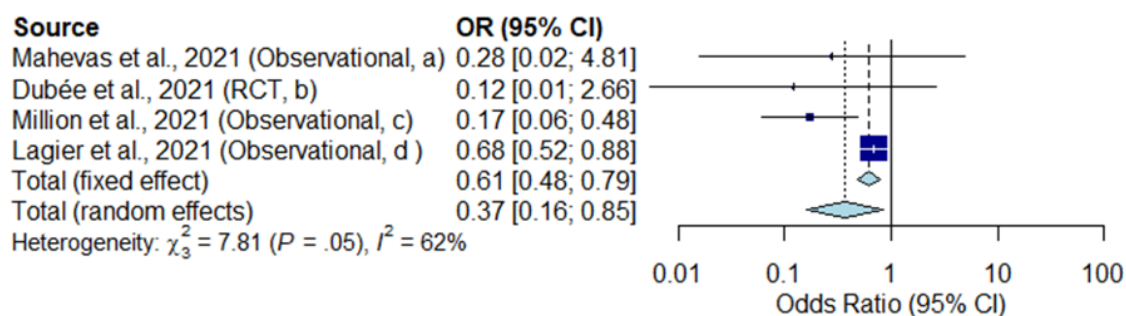


Figure C. Meta-analysis of French HCQ studies on COVID-19 mortality (a. moderate disease, death within 28 days, b. severe disease, death within 28 days, c. per-protocol, all deaths, d. Hazard ratio calculated by Inverse probability weighting (IPTW)-weighted analysis on the secondary population, time-to-death evaluated from admission. e. "as treated" effect, HCQ initially and after 48h, IPTW analysis, 21 days (weighted Hazard Ratio)). **Figure D.** Meta-analysis of French HCQ-AZ studies on COVID-19 mortality (a. calculated on numbers provided in the text: 0 deaths on 15 patients treated with HCQ-AZ, b. calculated on numbers provided in the supplementary data: 0 deaths or transfer to intensive care unit among 10 patients treated by HCQ-AZ at randomization. c. On 2,015 patients aged ≥ 60 years, d. Among 2,111 hospitalized patients).

C.



D.



*AZ: Azithromycin, HCQ: Hydroxychloroquine, OBS: Observational study, RCT: Randomized controlled trial,