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

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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-β) 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 planned study power is far to be reached. We calculated the IC 95% of the outcome in each arm. Death at 15 days in control 6/54 (11.11%) [IC 95: 2.73;19.49] and in HCQ 3/52 (5.77%) [IC 95: 0.00;12.11].The confidence interval is largely overlapping suggesting that the absence of difference between the two arms reported in their conclusion could be due to hazard alone. Confidence intervals should be given in such study as it informs readers on the possibility of inadequate sample size. These data should have been discussed in the paper.

Similarly, in another French trial multicentric RCT, HYCOVID [2], a placebo-controlled double-blind trial, 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%. Considering these two severely underpowered studies, 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, a significant decrease in the risk of mortality was found in both outpatients (-83% [3]) and inpatients (-32% [4]). The greater benefit in ambulatory patients underscores the importance of early management and treatment (<5 days after symptom onset), which has often been overlooked in RCTs (median time from symptom onset to randomization 9.0 days [interquartile range 7.0 - 12.0] in the DisCoVeRy trial [1]). Because type II error (β) is the failure to reject a false null hypothesis following a testing procedure (false negative), both studies at our center rejected the null hypothesis and thus cannot be suspected of insufficient power.

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. The number of patients in either sub-group here was too small, and the assignment to combination therapy not random, to warrant any statistical analysis. 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.

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 finished their studies to reject the null hypothesis to be able to conclude?

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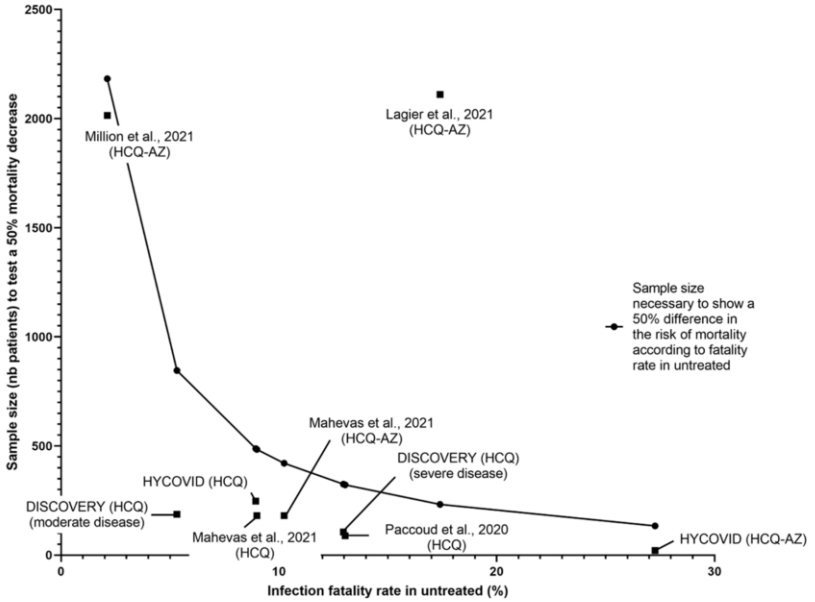
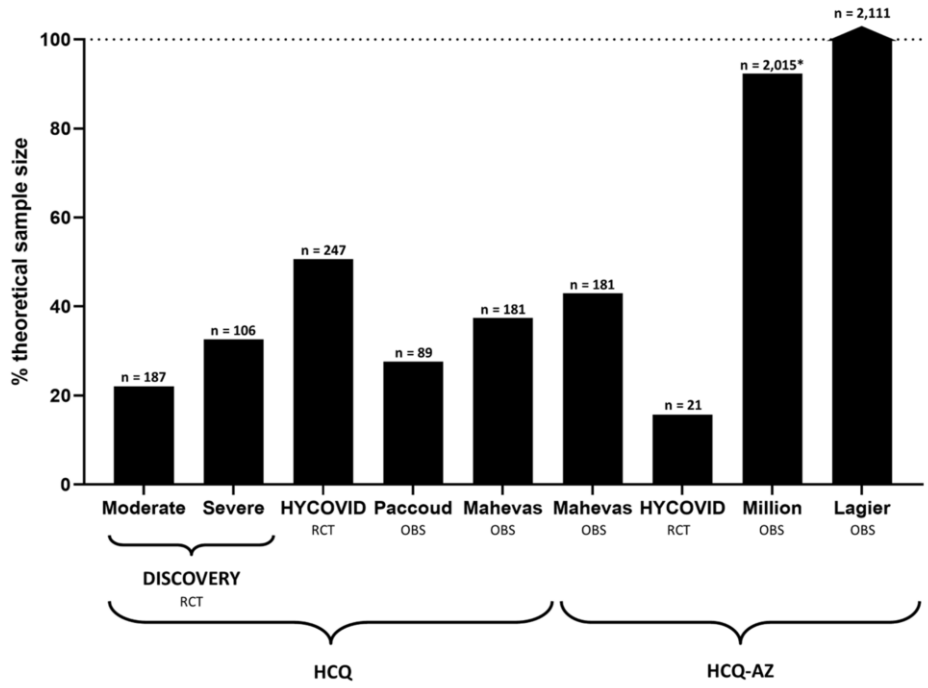
Figure. French studies were not designed to confirm HCQ and/or HCQ-AZ ineffectiveness on COVID-19 mortality

AZ: Azithromycin, HCQ: Hydroxychloroquine, OBS: Observational study, RCT: Randomized controlled trial, **A**. Sample size needed to test a 50% mortality risk difference according to infection fatality rate in untreated ($\alpha = 5\%$, $\beta = 80\%$), **B.** Percentage of the real sample size on the theoretical sample size needed to test a 50% mortality risk difference.

A.


Sample size (nb patients) to test a 50% mortality decrease
2500
2000
1500
1000
500
0
0
10
20
30
Infection fatality rate in untreated (%)
Million et al., 2021 (HCQ-AZ)
Lagier et al., 2021 (HCQ-AZ)
Sample size necessary to show a 50% difference in the risk of mortality according to fatality rate in untreated
Mahevas et al., 2021 (HCQ-AZ)
DISCOVERY (HCQ) (severe disease)
HYCOVID (HCQ)
DISCOVERY (HCQ) (moderate disease)
Mahevas et al., 2021 (HCQ)
Paccoud et al., 2020 (HCQ)
HYCOVID (HCQ-AZ)

B.


% theoretical sample size
100
80
60
40
20
0
n = 187
n = 106
n = 247
n = 89
n = 181
n = 181
n = 21
n = 2,015*
n = 2,111
Moderate
Severe
HYCOVID
RCT
Paccoud
OBS
Mahevas
OBS
Mahevas
OBS
HYCOVID
RCT
Million
OBS
Lagier
OBS
DISCOVERY
RCT
HCQ
HCQ-AZ

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