Response to: Comment on "Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients That Should be Ramped-Up Immediately as Key to the Pandemic Crisis"

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Conflicts of Interest: Dr. Risch acknowledges past advisory consulting work with two of the more than 50 manufacturers of hydroxychloroquine, azithromycin and doxycycline. This past work was not related to any of these three medications and was completed more than two years ago. He has no ongoing, planned or projected relationships with any of these companies, nor any other potential conflicts-of-interest to disclose.

I thank Dr. Fleury (1) for clarifying various details of one of the studies that I discussed in my review of efficacy and safety of outpatient medication treatment for COVID-19 patients (2). Dr. Raoult, the senior investigator of that study (3), has been carrying out a medically aggressive COVID-19 testing and treatment program in Marseille, France. From this distance, it can be difficult to glean all of the relevant details of the program and I appreciate Dr. Fleury's more local information and extended discussion.

In my analysis, I assumed that the patients described by Dr. Raoult as hospital patients were high-risk. In fact, it seems that Dr. Raoult's hospital base was used more as a clinic facility where outpatient testing and treatment were done, and for a fraction of the patients, full hospital admission occurred. Thus, Dr. Fleury is indeed correct that the 1,061 patients I discussed were not all high-risk. In the later published report of the Marseille cohort (4), the cohort is described as "909 inpatients in day-care hospital" and "152 inpatients in conventional units." The term "inpatients" here nominally conflates groups needing to be considered separately; these numbers were not contained in the preprint version (3) of the study that was originally available to me. Dr. Fleury says that the Marseille screening sample comprised "a general population sampling cohort that includes people as young as teenagers" (1), thus that expected numbers of deaths should be based upon general population COVID-19 mortality information. However, the tested Marseille subjects were all self-referred individuals, many from lower socioeconomic strata or recent immigrants, mostly with disease symptoms or known to have had exposure to people with symptoms, and their 152/1,061=14% "conventional unit" hospitalization suggests that at least this number would have been at high risk. A more exact number is difficult to determine though.

Fortunately, newly published information about this cohort suggests that the hydroxychloroquine-plus-azithromycin regimen does provide substantial outpatient treatment

benefit (5). The Marseille study now includes data from 3,737 outpatients among whom 3,119 were treated with hydroxychloroquine plus azithromycin for at least 3 days and 618 were treated with other methods, including the drug combination for less than 3 days, either of the medications alone, or neither one. Because the patients treated with hydroxychloroquine plus azithromycin were appreciably younger, had fewer comorbidities, and had less symptomatic disease than the patients treated with the other methods, the authors used multivariate logistic regression to carry out propensity-score exact subject matching on categories of both their modified Charlson combined comorbidity index and NEWS-2 (illness severity) scores. Using stratified Cox regression on that matched sample, they found that the hydroxychloroquine-plus-azithromycin treatment vs other treatment was associated with reduced mortality risk, HR=0.41 (95%CI 0.17-0.99), p=.048. The authors also noted that 88 of the 3,737 patients were not treated with the combined medications for a variety of potential cardiac contraindications, another 45 because of other possible drug interactions, that 12 treated patients stopped the medications early because of QTc prolongation, and that no instances of *torsades de pointes* or sudden death occurred. With the latest publication, the Marseille cohort data now more formally comprise one study of the many that have shown substantial benefit for treatment of high-risk COVID-19 outpatients with hydroxychloroquine plus azithromycin.

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