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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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Abstract

A major error is found in the article: Early Outpatient Treatment of Symptomatic, High_Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis, by Harvey Risch, which highlights how the work by Prof. Raoult should be read and considered.

Dr. Harvey Risch (1) advocated the use of hydroxychloroquine and azithromycin for the outpatient treatment of patients with coronavirus 19 (COVID-19). To support his case, he cited the mortality calculations from 2 cohorts, one presumably treated by Dr. Zelenko (2) in New York, and the other treated by Million et al.(3) in France. In his article, Dr. Risch made an error in the calculation of the estimated mortality among at-risk patients who were treated with a combination of hydroxychloroquine and azithromycin (and possibly also zinc). Indeed, in order to prove the supposed superiority of this bitherapy over standard care, Risch posited that based on the observed number of fatalities among at-risk patients in other studies, one would expect 20% of the 1,466 patients in these 2 cohorts to have died (i.e., approximately 293 patients rather than 7), and therefore the bitherapy of hydroxychloroquine plus azithromycin is 41 times more efficacious than standard of care.

After the initial online publication of Dr. Risch’s article, it came to light that 405 of these 1,466 patients were the at-risk patients in Dr Zelenko’s cohort; the remaining 1,061 comprised the whole sample in the study by Million et al. (3). However, as shown in their Table 2, not all of the 1,061 patients had at least 1 comorbid condition that was a risk factor. Adding the numbers of patients with each chronic condition reveals that less than 45% of the total treated sample had such a condition. In addition, because patients often have more than 1 comorbid condition (e.g., obesity and diabetes or obesity and hypertension), the number of patients who were really at risk is presumably far lower. 56 patients are even mere asymptomatic contacts of documented cases. Furthermore, the cohort has a striking demographic distribution: The mean age was 43.6 (standard deviation, 15.6) years, and the group included teenagers as young as 14 years of age. All of this is to say that the cohort in the study by Million et al. is in no way comparable to a typical cohort of hospital patients, who are generally older and in worse health. Moreover, a mean age of 44 years in a group with no children younger than 14 years of age indicates a very young cohort, much younger than average. When comparing the cohorts,
even patients with similar comorbid conditions do not have a similar magnitude of the risk. To be really at risk, you must be older.

Risch then multiplied 1,466 by 20% to get the expected number of deaths: 293. Here is where the error is manifest. It is indeed true that the fatality rate in hospitalized patients may be somewhere between 10% and 20%, as cited by Risch (1); however, there is no reason to expect a similar fatality rate in a cohort such as the one in the study by Million et al., even if it does contain elderly people and patients at risk. That cohort comprised patients who came on foot to queue up at the hospital, whereas in other hospitals, patients are generally admitted to the emergency department.

This points to the core of the problem in both the hospital procedures and the data in the article by Million et al. (3). The fatality rate of 10%–20% is a clinical fatality rate, which is usually calculated based on the number of hospitalized case patients. In France, this figure is 18%: Exactly 18,195 of 100,841 people had died of COVID-19 in hospitals as of May 20, 2020 (4).

Dr. Raoul, one of the other authors of the paper by Million et al., has widely publicized on television, the Internet, Twitter, and the like that he would test and treat everybody, and so he continues to do so with enormous support on social networks. This accounts for the strange demographic profile of his cohort: It is not a typical cohort of hospitalized patients, but rather a general population sampling cohort that includes people as young as teenagers. Because of this, the mean age of members of his cohort (3) appears close to the mean age of the general French population (42 years) (5), rather than the mean age of hospitalized patients (72 years) (4). The death toll in Raoult’s studies (3, 6) is not a clinical death toll but a general population death toll, and it should therefore be compared to estimated general population death tolls, which have been in the 0.5%–2% range when an entire population was examined (7), and it might even be as small as 0.37% as found in Germany in the study of the city of Gangelt (8) and not in the 20% range. It is clear that should one take a population with an actual clinical death toll of 18% and combine it with any number of mild or asymptomatic case patients who are resting at home, one would be able to lower the mortality rate to any small value, even as low as zero asymptotically. Stated otherwise, the selection of a young cohort artificially lowers the death rate enormously. It is known that the mortality rate among persons 70–80 years of age is approximately 30 times higher than that among persons 40–50 years of age, which explains the numbers reported by Dr. Risch (8). In addition, a 90-year-old man or woman who arrived on foot to queue up at the hospital in Marseille should not be counted in the same statistical stratum as a patient of the same age who arrived via ambulance receiving oxygen support.

This criticism is supported by the recent explanation by Dr. Raoult on his own television channel that he recruited hundreds of doctors to assess the COVID-19 status of patients via telephone calls (9) and also by his explanation that they have only 60 beds in the hospital in which he works, in which 37 patients died by the end of May 2020 (10). With 60 beds and a mean hospitalization time of at least a week, the expected number of patients who were actually hospitalized during the time of the clinical studies should be approximately 400, of whom 37 died. Therefore, the estimated clinical death toll in the Marseille cohort was approximately 10%. To state it flatly: The general death toll in the Marseille cohort is comparable to the known general death toll elsewhere, and the clinical death toll, which was never given, is likely to be comparable to the death toll among hospitalized patients elsewhere. It may be lower, but not by a factor 41 as posited by Dr. Risch.

In Dr. Zelenko’s cohort, the situation is less clear because as far as we know, the patients were not actually tested; they were also treated with zinc. In the Marseille data (6), when a general sampling of the population with mild or even no symptoms came to be tested, only 10% were found to be actually infected with COVID-19. If only 10% of the 405 at-risk patients in Dr. Zelenko’s cohort were actually
positive for COVID-19 (i.e., 40 persons) and if 20% of these should have died according to Risch (i.e., 8 persons), the number falls well within statistical insignificance.

In conclusion, the way the data were collected in Marseille is so peculiar (requesting people to come on foot and line up at the door for testing) that it fools everyone, including reputable experts, into believing that the mortality rate reported by Million et al. and more generally by Dr. Raoult on television and social media (sometimes 0.5% (11) and sometimes 0.9% (6)) is a clinical death toll, but it is not. Most patients were not in the hospital and were assessed at home by telephone (an estimate from the size of the cohorts and the number of beds suggests that only 10% of the patients were actually hospitalized). Therefore, it is closer to a general population death toll and should be appreciated as such. That Dr Raoult et al. find a mortality rate in the lower bound of the known general population mortality is easy to understand. The mean age of french population of age > 14 years is 48.5 years (obtained from data in Ref. 5). The cohort in Raoult’s work, as it happens, is even 5 years younger than the demographic average.

(1) Risch H A, Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis, American Journal of Epidemiology, to appear.


(5) France general demographic statistics from the National Institute of Statistics, INSEE, data available on line https://www.insee.fr/fr/statistiques/


(7) Fatality rate statistics in the general population, example of Iceland https://www.worldometers.info/coronavirus/country/iceland/


(10) Dr Raoult’s web TV broadcast https://www.youtube.com/watch?v=DZFN3DryH68

(11) Dr Raoult’s webTV broadcast
https://www.youtube.com/watch?v=zUbiYhknaK0&feature=youtu.be