Response to: "Concerns About the Special Article on Hydroxychloroquine and Azithromycin in High Risk Outpatients with COVID-19 by Dr. Harvey Risch"

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Running Head: Response to Fox et al.

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.

Fox et al. (1), characteristic of the disinformation that pervades reports on hydroxychloroquine (HCQ), make errors of fact, of interpretation, and crucial omissions about my work (2, 3). Given limited space, I discuss those most salient. The topic of their randomized-control-trial (RCT) "fundamentalism" has been discussed at length elsewhere (4-6).

First, Fox et al. cite Gautret et al. (7). This study has been subject to updated reinterpretations. Its evidence is unclear. It is negligible in the evidence base and reasonable not to include it.

The Brazil study of Esper et al. (8): "Dr. Risch's argument that those who chose to try the experimental treatment were sicker … seems unsupported." Fox et al. ignore subject characteristics in the study Table 1 (8), showing that the treatment group was older and had more diabetes, stroke and hypertension, and greater disease progression with higher frequencies of fever, cough, anosmia, diarrhea, headache, myalgia and dyspnea. The confounding is thus demonstrably against medication benefit, yet the study shows just such a significant effect.

Fox et al. cite the Skipper et al. (9) and Mitjà et al. (10) studies of outpatients, as supposed examples of "well-conducted randomized controlled trials." Both studies comprised essentially only low-risk subjects who do not generally get treated. As I have stated repeatedly (2, 3), only high-risk outpatients are relevant for studies of HCQ efficacy. These two studies are thus irrelevant.

The second Mitjà et al. RCT (11), while also mostly low-risk subjects, included 293 high-risk nursing-home residents. In them, HCQ cut the primary outcome, post-exposure PCR-positive infection, in half.

In considering new studies, Fox et al. cite only two, and they are also irrelevant. The first (12): "These were hospitalized patients but almost all (148 of 150) had mild to moderate coronavirus."

Fox et al. fallaciously equate “mild-to-moderate” hospitalized disease with outpatient disease. These study subjects were on average randomized on symptom day-17, whereas outpatient treatment must start by day-5. The second study (13) was also of hospitalized inpatients and irrelevant for outpatient considerations as noted elsewhere (14, 15).

Meanwhile, Fox et al. ignore the mortality analysis of 199 PCR-positive Marseille outpatients, all > 60, matched to controls of similar disease severity and chronic risk factors, who either did not take HCQ+azithromycin or took it for <3 days (16). Treated subjects had 59% reduced mortality risk, *P*=.048.

Fox et al. ignore a Brazil study (3) of 717 consecutive COVID-positive HMO outpatients starting treatment within the first five days, with HCQ, other drugs, or none, at physician discretion. Adjusted for age, gender, dyspnea, obesity, diabetes, heart disease and other medications, HCQ cut hospitalization risk 55%, *P*=.0065.

Fox et al. ignore the study of 226 infected residents in 23 nursing homes in Marseille (17). In multivariate analysis adjusted for sex, age and detection modality, receipt of HCQ+azithromycin 3+ days was associated with 59% reduced mortality risk, *P*=.017.

Fox et al ignore a New Jersey study of 1,274 PCR-positive patients with non-admission ER visits, among whom 97 took HCQ, and from the remaining 1,177, 970 were propensity-score matched by age, demographic variables and a host of comorbidity factors, presenting symptoms, indicators of disease severity, baseline laboratory tests, and ER-visit and follow-up times (18). In matched multivariate analysis, HCQ cut hospitalization risk by 47%, *P*=.038.

Fox et al. don’t include the Andorra study (19) in which all 100 COVID-19-confirmed patients identified in a long-term care institution were followed for mortality. In analysis adjusted for

degree of disease progression, treatment with HCQ+azithromycin was significantly associated with more than ten-fold reduced mortality.

Finally, Fox et al. don't include the 7,892 symptomatic SARS-CoV-2 tested-positive patients in Saudi Arabia in its universal healthcare clinics (20). All patients received daily zinc sulfate; 3,320 also received HCQ and 4,572 standard care. Seven patients died in the HCQ group and 54 in the standard-care group, the mortality reduced 5-fold, $P=10^{-4.7}$, with HCQ.

These studies comprise all relevant controlled trials available to-date and all are significant. There is plenty more of other types of evidence. When early treatment of high-risk outpatients is strictly considered and not misrepresented, as Fox et al. do, with studies of low-risk or hospitalized inpatients, all of the evidence shows benefit with HCQ use.

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