**Hydroxychloroquine treatment does not reduce COVID-19 mortality; underdosing to the wrong patients? – Authors' reply**

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We thank Luis Ayerbe and colleagues for the opportunity to further discuss our Article.1 The choice of our study population—individuals with rheumatoid arthritis or systemic lupus erythematosus—was made to minimise the potential for confounding by indication when estimating the effectiveness of hydroxychloroquine use rather than investigating how to prevent severe COVID-19 in this population. The key question is whether our study had sufficient statistical power to detect a real difference in mortality, if one existed? As stated in the Article, the CIs around our key estimate (hazard ratio 1·03 [95% CI 0·80–1·33]) suggested that we could exclude substantial benefit, although a modest benefit or harm on a relative scale could not be ruled out; therefore, trials were warranted. Ayerbe and colleagues suggest that hydroxychloroquine might be differently effective or ineffective in specific demographics: we note that 25% of those in our study were aged over 75 years and, as reported, we found no evidence of effect modification by age.

Ayerbe and colleagues criticise our Article for not citing two systematic reviews, both of which were published or preprinted after the cutoff date for our literature search. The systematic review by Fiolet and colleagues2 included studies published before July 25, 2020, investigating hydroxychloroquine as treatment in patients who were hospitalised using mean daily doses between 333 and 945 mg. They did not observe any mortality benefit associated with hydroxychloroquine alone; however, there were apparent harms when combined with azithromycin, something we were unable to assess in our data. Fiolet and colleagues2 also did a subgroup analysis of studies that used therapeutic doses of more than 500 mg per day, which also found no benefit or harm associated with hydroxychloroquine (pooled relative risk [RR] 1·04 [95% CI 0·83–1·31]). Similarly, the cited meta-analysis by Di Castelnuovo and colleagues3—published as a preprint—found no association between hydroxychloroquine and mortality in studies using doses of more than 400 mg per day (pooled RR 1·05 [0·73–1·53]).

Our study investigated hydroxy- chloroquine as pre-exposure prophy- laxis as opposed to post-exposure prophylaxis or therapy. Of note, five randomised trials on hydroxychloroquine prophylaxis have been published; four are summerised in the meta-analysis by Lewis and colleagues,4 with a fifth trial done by Barnabas and colleagues.5 Only one of these was considered in reviews by Fiolet and colleagues and Di Castelnuovo and colleagues. All five trials have consistently shown no prophylactic benefit of hydroxychloroquine across varied contexts and dosing regimens.

Most of the high-quality evidence for hydroxychloroquine being used as treatment of COVID-19 or as pre-exposure or post-exposure prophylaxis suggests no mortality, nor any other, benefit; however, many report toxicities, such as cardiac arrhythmia or QTc prolongation, and several report increased mortality risk. To suggest hydroxychloroquine, or any medical product, could offer benefit at particular doses or phases of infection, let alone in specific sociodemographic groups, requires careful pharmacoepidemiological investigation and, ideally, randomised trials. Because the evidence to date increasingly suggests no beneficial role for hydroxychloroquine for either treatment or prophylaxis, we believe ongoing hydroxychloroquine studies should be reported, but that future studies and resources would be better focused on other emerging possible treatments.

The declaration of interests remains the same as in the original Article.

**References**

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