Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Hydroxychloroquine treatment does not reduce COVID-19 mortality; underdosing to the wrong patients?

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An observational study published in *The Lancet Rheumatology* by Christopher T Rentsch and colleagues[1] showed no association between pre-exposure use of hydroxychloroquine and reduced mortality in patients with COVID-19 who also have systemic lupus erythematosus or rheumatoid arthritis. 138 440 (71·1%) participants were women, and the study population was relatively young, with 50% of the participants younger than 66 years. In a previous study,[2] the death rate in patients younger than 70 years was low, and it was lower for women than men; therefore, the differences in mortality might be very difficult to appreciate in the study by Rentsch and colleagues,[1] in which half of the participants are under 70 years old and more than two thirds are women. Rentsch and colleagues[1] did not reference any of the several large peer reviewed studies showing an association between hydroxychloroquine and lower mortality in patients with COVID-19, or the systematic reviews that have critically appraised and summarised these studies.[3,4] These studies were all disregarded as methodologically weak, and an opportunity to build upon the interesting aspects of previous research was missed. Rentsch and colleagues[1] mentioned that the dose at which hydroxychloroquine is given for systemic lupus erythematosus (SLE) and rheumatoid arthritis is similar to the one used in an ongoing clinical trial (NCT04303507) for prevention of COVID-19 (200–400 mg per day). However, even when hydroxychloroquine is used at maximum dose, patients with SLE or rheumatoid arthritis do not receive doses as high as those used in patients with COVID-19 in studies that showed an association between hydroxychloroquine and reduced mortality (800 mg on day 1 followed by 400 mg a day for four days).[3,4] The large number of studies on hydroxychloroquine that show contradictory results on different outcomes of COVID-19 might reflect the methodological limitations of each study on both sides of the debate. It could mean that hydroxychloroquine might only be beneficial at a certain dose, in specific phase of the disease, or in patients with a particular sociodemographic or clinical profile. Like Rentsch and colleagues,[1] we think that additional studies are required on the potential benefit of hydroxychloroquine, which is economical, has not proven to be harmful at the dose used for COVID-19, and could be prescribed to ambulatory patients right after the diagnosis before they develop respiratory distress.

We declare no competing interests.

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1 Rentsch CT, DeVito NJ, MacKenna B, et al. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. *Lancet Rheumatol* 2021; **3:** e19–27.

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Authors' reply

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 colleagues[2] 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 colleagues[1] 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 colleagues[3]—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 hydroxychloroquine as pre-exposure prophylaxis as opposed to post-exposure prophylaxis or therapy. Of note, five randomised trials on hydroxychloroquine prophylaxis have been published; four are summarised 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.

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1 Rentsch CT, DeVito NJ, MacKenna B, et al. Effect of pre-exposure use of hydroxychloroquine on COVID-19 mortality: a population-based cohort study in patients with rheumatoid arthritis or systemic lupus erythematosus using the OpenSAFELY platform. *Lancet Rheumatol* 2021; **3:** e19–27

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