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Authors' response

We thank Barde *et al*¹ for critically going through the research we published². Our sampling strategy allowed us to recruit participants having elements of evenness till the point they got tested for SARS-CoV-2. It was important to consider this aspect and take it into account because, in any case-control investigation, the cases that become available for inquiry come to medical attention due to various preceding selection factors and recruitment of controls should keep such considerations into account. The ICMR-COVID-19 data portal helped us in doing so and to sample cases and controls from the pool of symptomatic healthcare workers (HCWs) who were tested for SARS-CoV-2. This helped in reducing potential sampling biases. It was worth considering in this context that the reasons for asymptomatic HCWs getting tested for SARS-CoV-2 could potentially be different and heterogeneous from the symptomatic ones. However, this is not to say that the results would remain the same, had we considered including cases from the pool of infected but asymptomatic HCWs. We would further add that the evidence generated though one million tests conducted during January through April 2020 in India showed that about 28 per cent of all SARS-CoV-2-positive cases were asymptomatic³ - presenting a different picture from what the authors of the letter suggested.

Interestingly, one could trace the unfolding saga of HCQ in COVID-19 as far back as in February 2020, when the State Council of China, in a news conference, indicated the efficacy of HCQ in COVID-19⁴. The results from the study by Gautret *et al*⁵ as well as several other analyses highlighting the use of HCQ

in COVID-19 started making rounds on social media much before the first version of the HCQ prophylaxis advisory was released by the COVID-19 National Task Force in India^{6,7}. The enthusiastic media coverage of US President Donald Trump's endorsement of HCQ for COVID-19 was also headline news since mid-March 2020. With such incidents, and the ability to purchase HCQ over the counter, we would not be surprised if a proportion of the HCWs were self-medicating prior to the release of the advisory. While we acknowledge that the usual limitations of self-reported data continue to be applicable to our dataset, it was not inconceivable that a small proportion of the HCWs had consumed six or more doses by the time our recruitment period closed. Further, as highlighted in our methods section, the cases and controls were matched for location (testing centre) and temporality (testing date). We decided not to match on variables such as gender and age to avoid the risk of overmatching, as it had been observed that such demographic factors were associated with SARS-CoV-2 infection, and we could not rule out if they were situated along the causal pathway⁸.

We appreciate the observation that the subgroup analysis may have smaller sample sizes and reiterate the need for larger clinical trials to provide definitive evidence to resolve some of the dilemmas. Given the restrictions of working within a pandemic setting, and the need to generate evidence rapidly, keeping pace with the changing epidemiology of COVID-19, we acknowledge such limitations.

The current case-control investigation was designed in the context of prophylaxis against acquisition of SARS-CoV-2 infection and not for treatment of COVID-19. As such, we find no contradiction between the findings in our study and the recommendations for the management of COVID-19. At this juncture, we maintain that the findings are indicative of an association between HCQ prophylaxis and protection against SARS-CoV-2 infection, and would also like to address the popular misconception that if a 95 per cent confidence interval (CI) includes the null value and another excludes it, the interval excluding the null is the more precise one. The precision of the statistical estimation, however, is measured by the width of the CI (which was narrow in our study, and therefore, indicative) and not solely guided by the inclusion of

the null or any specific value⁹, let alone its appearance with a specific *P* value.

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