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Correspondence

Interpreting the impact of hydroxychloroquine prophylaxis on SARS-CoV-2 infection

Sir,

We read with interest the study by Gupta *et al*[1] which presented the findings of SARS-CoV-2 seroprevalence in a large cohort of healthcare workers (HCWs) from a tertiary healthcare facility in north India and examined the effect of various infection control measures. Various strategies were adopted during the SARS-CoV-2 pandemic for reducing transmission as a result of occupational exposure among HCWs. One such strategy included search for medication that would reduce this risk by repurposing of existing drugs[2]. Among these, hydroxychloroquine (HCQ) has attracted the attention of the scientific community globally, and there are many studies supporting or refuting the efficacy of HCQ in providing effective prophylaxis to those at a high risk of contracting the disease[3-7].

HCQ prophylaxis was recommended by the ICMR National Task Force for COVID-19 for asymptomatic HCWs exposed to COVID-19 patients and asymptomatic household contacts of COVID-19 patients[8]. HCQ elevates the *p*H of endosomes and inhibits SARS-CoV-2 RNA-mediated inflammatory response[9].

Gupta *et al*[1] reported that there was no difference in seropositivity between the subgroup of HCWs who did/did not receive the HCQ pre-exposure prophylaxis. Further, around 45 per cent of HCWs who developed antibodies against SARS-CoV-2 in the study were asymptomatic. Since the information on the percentage of HCWs who were on HCQ prophylaxis and asymptomatic despite developing seropositivity is lacking, this precludes commenting on the ability of HCQ in preventing clinically apparent disease in those who took the medication prophylactically. The present study[1] also has not taken into account the adequacy of doses of HCQ consumed by the HCWs which is considered to be protective as reported in a case–control investigation conducted by Chatterjee *et al*[10].

Findings from our cross-sectional serosurveillance study[11] has suggested that pre-exposure prophylaxis with HCQ may have a role in reducing the vulnerability to infection as depicted by the univariate and multivariate analysis [adjusted odds ratio (OR) 0.55, 95% confidence interval (CI) 0.3-0.9, *P*=0.047]. The HCWs who took HCQ were divided into four groups – no HCQ and intake of HCQ for <6, 6-10 and >10 weeks. Running the HCQ prophylaxis numbers through logistic regression, for each increasing category of HCQ use, there exists a dose–response OR=0.70 (95% CI 0.50-0.99, *P*=0.032). This trend is much stronger among the ever-exposed categories (*i.e*., excluding the never-used HCQ people), per-category OR=0.27 (95% CI 0.11-0.65, *P*=0.0036)[11]. Two other observational studies from India[12,13] have supported the evidence in favour of HCQ pre-exposure prophylaxis. All these observational studies from India taken together enrolled a total of 2660 participants and provided a corroborative evidence of the effectiveness of HCQ prophylaxis for frontline HCWs.

Although Gupta *et al*[1] have reported findings which do not suggest any added benefit of the use of HCQ as prophylaxis among HCWs, analyzing the relationship between the number of doses of HCQ consumed and seropositivity and the severity of disease among those who developed symptoms while on HCQ prophylaxis may be helpful in further refining the analysis. This might be particularly useful in the current situation of ongoing pandemic, with measures such as social distancing becoming increasingly difficult to practise and the vaccine yet to reach the masses.

***Conflicts of Interest*:** None.

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Authors' response

We thank Yadav and Madkaikar for reading our article with interest and commenting regarding prophylactic use of hydroxychloroquine sulphate (HCQS) in asymptomatic healthcare workers (HCWs). Yadav *et al*[1] raised a relevant point that perhaps the HCQS prophylaxis reduced or abated symptomatic disease, the duration and dosage of HCQS prophylaxis influenced the outcome.

We reported that 769 HCWs received HCQS prophylaxis and 99 of 769 were seropositive compared to 388 of 2970 HCWs who did not receive HCQS prophylaxis (P=0.89)[2]. On analyzing the correlation of symptomatic disease with HCQS prophylaxis, it was found that among the seropositive HCWs, 70.77 per cent (70/99) of those who received HCQS prophylaxis were symptomatic compared to 52.3 per cent (203/388) HCWs who were not on HCQS prophylaxis (P<0.01). In our study, higher numbers of HCWs with HCQS were symptomatic compared to those who did not take the HCQS prophylaxis, and thus, the HCQS prophylaxis did not seem to improve upon the symptomatic status in HCWs[2]. Yadav *et al*[1] have reported the presence of symptoms in comparable numbers of patients with or without HCQS prophylaxis (39.78 vs. 35.3%; P=0.3).

Another relevant comment was on the correlation of the duration and dosage of HCQS prophylaxis with the likelihood of seropositivity or RT-PCR–positive SARS-CoV-2 infection. In this regard, Chatterjee *et al*[3] have reported a relatively fewer numbers of

HCWs infected with SARS-CoV-2 in the subgroup who received more than six doses of HCQS (n=12), whereas the difference in incidence was not different in those who received less doses of HCQS. Goenka *et al*[4] reported lower seroprevalence for SARS-CoV-2 in those who received adequate, *i.e*., more than six doses of HCQS versus rest of the HCWs. However, we have concerns regarding the interpretations in the study by Yadav *et al*[1]. First of all, the data shown for comparison within seropositive subjects (n=55) are for HCQS exposure of <4h versus >4h versus no HCQS, whereas the HCWs with HCQS prophylaxis were otherwise divided into those with <6, 6-10 and >10 wk of HCQS. The criterion on how the patients were divided into HCQS exposure of <4h versus >4h is not mentioned in this paper. Further, the data on dosage and duration of HCQS prophylaxis were not available in 36.2 per cent (101/279) of the HCWs in this study who were excluded from the subgroup analysis. As a result, the patients in the seropositive group on HCQS prophylaxis (<22; exact numbers not mentioned) in this study were perhaps too few for a meaningful subgroup analysis when split into three further subgroups[2].

A few randomized controlled trials of HCQS as pre or post-exposure prophylaxis for COVID-19 suggested that HCQS did not significantly reduce laboratory confirmed COVID-19 or COVID-19–compatible illness among HCWs[5-7]. Kumar *et al*[8] and Kashour *et al*[9] in their meta-analysis studies also concluded that HCQS therapy for COVID-19 lacked efficacy in reducing short-term mortality in patients hospitalized with COVID-19 or risk of hospitalization in outpatients with COVID-19 and was associated with an increase in mortality and the negative effects were more pronounced in the hospitalized patients.

On March 28, 2020, the Food and Drugs Administration (FDA) granted emergency use authorization (EUA) for hydroxychloroquine as a COVID-19 prophylaxis. The emerging scientific data suggest that dosing for HCQS is unlikely to kill or inhibit the SARS-CoV-2 virus, and on June 15, 2020, the FDA revoked EUA to use HCQS and chloroquine to treat COVID-19 in hospitalized patients[5-10]. FDA also cautions against the use of HCQS for COVID-19 outside of the hospital setting or in a clinical trial due to risk of heart rhythm problems[8-10]. Therefore, use of HCQS for its potential benefits in COVID-19 does not outweigh its known and potential risks.

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