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Authors' response

We thank the authors of the letter for their critical reading of our case-control investigation[1]. During this investigation, we matched the cases and controls by time and location using the date of testing and laboratory where they were tested following the development of symptoms of respiratory tract infection, to limit the variability between cases and controls. The overall purpose of our investigation was to identify factors associated with SARS-CoV-2 infection (protective or risk posing). However, we realize that examining the safety and efficacy of pre-exposure prophylaxis, based on hydroxychloroquine (HCQ), would require clinical trials as indicated in the discussion section of our article[1].

Chloroquine (CQ) and HCQ are known to have extensive tissue spread, resulting in a large volume of distribution in the human body. Single-dose kinetics studies in the context of malaria chemoprophylaxis show that adequate plasma levels of chloroquine may be achieved only after four weeks. During this period, the individual taking CQ prophylaxis may not achieve the desired plasma concentration of the drug needed for protection[2]. These findings prompted the recommendation that CQ prophylaxis in malaria-naïve travellers be initiated at least two weeks prior to entry into malaria-endemic areas. Interestingly, our study also provided a similar hint of protection against SARS-CoV-2 infection obtained through HCQ chemoprophylaxis, where a dose-response relationship appeared unfolding after the intake of four or more maintenance doses following the initial loading dose.

Importantly, although CQ and HCQ are efficiently concentrated in lung tissue over time, reaching at least 11.8 times the concentration in plasma, *in vivo* concentrations needed to counter SARS-CoV-2 infection, may be achieved in a dose-dependent manner[3,4]. For a drug like HCQ where lysosomal sequestration is known and can lead to variable concentrations in various body tissues compared to plasma levels[5], information regarding HCQ levels, specifically in lung tissues, is important as far as the activity against SARS-CoV-2 and other respiratory viruses is concerned. With the current evidence, it is unclear if parameters such as area under the curve (AUC) can be reliably used to predict levels in respiratory tissues and drug efficacy[6].

As our study was specifically conducted to identify the associations between various exposure variables and SARS-CoV-2 infection in symptomatic healthcare workers (HCWs), it would be inappropriate to extrapolate the findings to home-based contacts of confirmed cases of COVID-19. Notwithstanding the findings of our study, we would still like to underscore the necessity of pondering over protective behavioural factors and appropriate use of personal protective equipment along with plausible chemoprophylaxis-based biologic intervention while examining the occurrence of SARS-CoV-2 infection in HCWs.

Pranab Chatterjee[1], Tanu Anand[7], Kh. Jitenkumar Singh[2], Reeta Rasaily[3], Ravinder Singh[4], Santasabuj Das[8], Harpreet Singh[5], Ira Praharaj[6], Raman R. Gangakhedkar[6], Balram Bhargava[†] & Samiran Panda[9,*]

[1]Translational Global Health Policy Research Cell, [†]Department of Health Research, Ministry of Health & Family Welfare, New Delhi 110 001, [2]ICMR-National Institute of Medical Statistics, [3]Division of Reproductive Biology, Maternal Health & Child Health, [4]Division of Non-Communicable Diseases, [5]Informatics, Systems & Research Management Cell, [6]Division of Epidemiology & Communicable Diseases, [7]Multidisciplinary Research Unit/Model Rural Health Research Unit, [†]Indian Council of Medical Research, New Delhi 110 029, [8]Division of Clinical Medicine, ICMR-National Institute of Cholera & Enteric Diseases, Kolkata 700 010, West Bengal & [9]ICMR-National AIDS Research Institute, Pune 411 026, Maharashtra, India

[*]*For correspondence*: director@nariindia.org

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