**Comments**

**Title:** The ICMR bulletin on targeted hydroxy-chloroquine prophylaxis for COVID-19 needs to be interpreted with caution.

**Author and affiliation:**

\*Migita D’cruz, M.D.

Senior Resident

Geriatric Clinic and Services

Department of Psychiatry

National Institute of Mental Health and Neurosciences (NIMHANS)

Bangalore 560 029, India

Email: [migitadcruz@gmail.com](mailto:migitadcruz@gmail.com)

**Main text:**

Dear Editor

The bulletin from the National Task Force for COVID-19 of the Indian Council of Medical Research (ICMR) dated 23/03/2020 recommends the use of hydroxy-chloroquine for prophylaxis in (1) asymptomatic health care workers involved in the care of suspected and confirmed patients and (2) household contacts of confirmed patients, with the viral infection. [1] This is cause for concern, both with regard to bioethics and good clinical practice.

The recommendation is based upon recent evidence of the repurposed anti-malarial drug, derived from preliminary studies, in the wake of the pandemic. [2] [3] [4]

Open label studies have demonstrated significantly better clinical outcomes and virus clearance rates in patients with confirmed COVID-19 infection (regardless of clinical status), when treated with hydroxy-chloroquine as opposed to controls. A combination of hydroxy-chloroquine and azithromycin appears to be superior in terms of both these outcomes, when compared to hydroxy-chloroquine alone. [5]

Cell culture studies, in addition, have demonstrated reduced replication by the SARS-CoV-2 in infected cell culture lines treated with hydroxy-chloroquine alone, and a combination of remdesivir and hydroxy-chloroquine. [6]

The expert consensus derived from these preliminary studies is that hydroxy-chloroquine limits the replication of the SARS-CoV-2 in vitro and improves clinical outcomes in vivo and recommends further clinical studies to explore its role in prophylaxis and treatment. As of March 1, 2020, there appear to be 23 registered ongoing clinical trials to this extent, across the world. [7] [8] While this preliminary evidence is heartening, there is need for caution admixed with the optimism.

Firstly, there is not, as of yet, definitive pre-clinical or clinical evidence demonstrating the efficacy of hydroxy-chloroquine as a prophylactic agent for COVID-19. [9] [10] Sixteen to twenty percent of patients with the infection, may be asymptomatic. [5] [11] However, transmission rates, though estimated to be high, are unclear. While asymptomatic patients may transmit upto 10 % of the infection, it would be inappropriate to initiate treatment in the absence of definitive evidence of COVID-19 infection. [12] [13]

Secondly, drug pharmacokinetics in special populations such as children (less than 12 years), the elderly; and expectant and lactating mothers differ considerably from the general population. [14] They are also at greater risk of adverse effects due to hydroxy-chloroquine. Considering that special populations are at higher risk of developing any infection, the drug may be least applicable in patients where it is the most required. [9] The logistic issues surrounding the conduct of research in these populations is acknowledged, as is the urgency for containment of the spread of the infection in the community. [15] Despite this, the use of the drug, particularly in these subsets merits extreme caution, optimal dose titration and close monitoring.

Thirdly, the drug is also contraindicated in patients at risk of, or suffering from retinopathy, maculopathy, glucose 6 phosphate deficiency and QTc prolongation [5]. Azithromycin, when combined with hydroxy-chloroquine, appears to have a cumulative effect upon the QTc interval. [5] The ICMR has not, in their bulletin addressed these contraindications or how to screen for them prior to drug administration.

Upon a partly related note, the bulletin, meanwhile, has been interpreted, considerably out of context by both the health care profession and the lay population, several of whom appear to have procured the drug over the counter or with self-prescriptions and medicated themselves and contacts for prophylaxis. This has led to both the shortage of what is an essential medication for the treatment of malaria and auto-immune conditions, and to reports of maculopathy and cardiac arrest in vulnerable individuals. [16]

Thus, there appears to be inadequate clinical evidence, as of now, to warrant the use of hydroxy-chloroquine for prophylaxis. Further, the risk-benefit ratio of drug administration needs to be closely examined, particularly in those vulnerable to adverse drug reactions. The clinical contraindications need to be explicitly addressed in public health information, as must caution against self-administration. A better strategy may be to enhance testing of asymptomatic contacts and consider the administration of the hydroxy-chloroquine on a case by case basis, while awaiting results of the clinical trials that are underway. [17]

The WHO and the FDA have not found conclusive evidence to support the recommendation of any drug for the treatment or prophylaxis of COVID-19 and consider hydroxy-chloroquine experimental therapy. It is recommended that the administration of the drug, therefore, be considered with due regard for Section 12 of the ICMR guidelines for research during humanitarian emergencies and disasters and the Good Clinical Practice Guidelines for Clinical Research in India by the Central Drugs Standard Control Organization (CDSCO).

**Exclusive licences:**

*“The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors,* [a worldwide licence](http://www.bmj.com/sites/default/files/BMJ%20Author%20Licence%20March%202013.doc) *to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.”*

**Transparency declaration**

The lead author\* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

\*The manuscript’s guarantor.

**Conflict of Interest:** Dr. D'cruz has nothing to disclose.

**Patient and Public Involvement:**

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

**References:**

1. Advisory on the use of Hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. Indian Council of Medical Research. 2020 March 23. Available from: <https://icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM_V2.pdf>

2. Harrison C. Coronavirus puts drug repurposing on the fast track. Nature Biotechnology. 2020 Feb 27. Available from: <https://www.nature.com/articles/d41587-020-00003-1>

3. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. International Journal of Antimicrobial Agents. 2020 Mar;105932. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/32145363>

4. Faccenda E, Armstrong JF, Davenport AP, Harding SD, Pawson AJ, Southan C & Davies JA. Coronavirus Information. IUPHAR/BPS Guide to Pharmacology. Retrieved from <https://www.guidetopharmacology.org/coronavius.jsp>

5. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. 2020 Mar 20; 105949. Available from: <https://www.sciencedirect.com/science/article/pii/S0924857920300996>

6. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research. 2020 Mar; 30(3):269–71. Available from: <https://www.nature.com/articles/s41422-020-0282-0>

7. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. Journal of Critical Care. 2020 Mar 10; Available from: <http://www.sciencedirect.com/science/article/pii/S0883944120303907>

8. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. Multicentre collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020 Mar 12; 43(3):185–8; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/32164085>

9. CDC. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. 2020 [cited 2020 Mar 25]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>

10. Coronavirus disease (COVID-19) technical guidance: Patient management. World Health Organization. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management>

11. Kenji Mizumoto, Katsushi Kagaya, Alexander Zarebski, Gerardo Chowell. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillanc. March 12, 2020. Available from: <https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180>

12. Coronavirus Spreads Quickly and Sometimes Before People Have Symptoms, Study Finds. UT News. 2020 March 16. Available from: <https://news.utexas.edu/2020/03/16/coronavirus-spreads-quickly-and-sometimes-before-people-have-symptoms-study-finds/>

13. Berger ZD, Evans NG, Phelan AL, and Silverman RD. Covid-19: control measures must be equitable and inclusive. BMJ [Internet]. 2020 Mar 20 [cited 2020 Mar 25]; 368. Available from: <https://www.bmj.com/content/368/bmj.m1141>

14. Guidelines for the Treatment of Malaria. 3rd edition. Geneva: World Health Organization; 2015. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK294433/>

15. Lessons from the frontline of the covid-19 outbreak. The BMJ. 2020. Available from: <https://blogs.bmj.com/bmj/2020/03/20/lessons-from-the-frontline-of-the-covid-19-outbreak/>

16. Pharmacists blame Donald Trump for shortage of hydroxychloroquine. Manjeet Sehgal India Today. 2020 March 24. Available from: <https://www.indiatoday.in/india/story/pharmacists-blame-donald-trump-for-shortage-of-hydroxychloroquine-1659312-2020-03-24>

17. Watkins J. Preventing a covid-19 pandemic. BMJ. 2020 Feb 28; 368. Available from: <https://www.bmj.com/content/368/bmj.m810>

18. National Ethical Guidelines for Biomedical and Health Research involving human participants. Indian Council of Medical Research. 2017 Oct. Available from: <https://www.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf>

19. Good Clinical Practice Guidelines for Clinical Research in India. Central Drugs Standard Control Organization. 2001. Available from: <http://www.sgpgi.ac.in/sop/GCP-%20Indian.pdf>