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Chloroquine or hydroxychloroquine for prophylaxis of COVID-19

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In-vitro studies have shown that chloroquine is effective against several viruses, including severe acute respiratory syndrome coronavirus (SARS-CoV).[1] Multiple mechanisms of action have been identified for chloroquine that disrupt the early stage of coronavirus replication. Moreover, chloroquine affects immune system activity by mediating an anti-inflammatory response, which might reduce damage due to the exaggerated inflammatory response.[1] At the time of the SARS epidemic, chloroquine was suggested as a drug that could be used to treat this infection.[2] However, randomised, double-blind, controlled studies in humans to evaluate its efficacy for this use were not done, and the true clinical efficacy of chloroquine in treating coronavirus infections was not established.

Because coronavirus disease 2019 (COVID-19) is associated with substantial morbidity and mortality,[3] and no specific pharmacological treatment that is effective against it is available, chloroquine and chloroquine-related formulations have been tentatively included among drugs for use in limiting the total burden of COVID-19.[4,5] However, no studies have evaluated the use of chloroquine for prophylaxis.

Chloroquine is a cheap drug that has been used for decades—predominantly for malaria prophylaxis, for which it had excellent results and good safety and tolerability.[1] Severe adverse events, which mainly involve retinal and psychiatric symptoms, occur only when doses prescribed for malaria are substantially higher than required.[1] Inhibition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication seems essential to reduce the risk of spread and development of COVID-19. SARS-CoV-2 is highly contagious.[5] Most people who live in areas with a high incidence of COVID-19 are apparently healthy, but they can be SARS-CoV-2 negative and healthy or healthy but with asymptomatic infection. In both cases, effective drugs such as chloroquine and its related formulations might prevent infection (ie, in those who are SARS-CoV-2 negative) or the development of severe symptomatic disease (ie, in those who are SARS-CoV-2 positive and asymptomatic or with minor symptoms), substantially reducing morbidity and mortality due to COVID-19. The dose used might be the same as that usually administered for malaria treatment given chloroquine inhibited SARS-CoV replication at a 50% effective concentration of 8·8 μmol/L. The half-maximal inhibitory concentration (IC_{50}) of chloroquine inhibition of SARS-CoV replication in Vero E6 cells, 8·8 μmol/L, is substantially lower than the plasma concentrations that are reached in humans when the drug is prescribed to treat malaria at a dose of 25 mg/kg over 3 days.[1] For long-term prophylaxis, even lower doses could be used. Doses of 3·6 mg/kg, similar to those generally prescribed to treat rheumatoid arthritis, lead to plasma concentrations of 1–3 μmol/L—ie, the same concentration range as the IC_{50} for SARS-CoV inhibition.[1] Alternatively, hydroxychloroquine could be used, for which even greater efficacy has been reported in in-vitro studies.[5] Prophylaxis could last for the whole duration of an outbreak, and in countries in which malaria is not endemic, there is no risk of negative events associated with the development of resistance to this drug. In countries where malaria is endemic, appropriate monitoring of resistance among *Plasmodium* spp is needed.

Future studies might better elucidate the most effective schedule of administration and potential adverse events. We advocate for studies to evaluate whether chloroquine or hydroxychloroquine prophylaxis should be considered in a country such as Italy, where there are thousands of cases and deaths as a result of COVID-19.

We declare no competing interests.

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1 Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 2003; **3:** 722–27.
2 Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. *Pharmacol Res Perspect* 2017; **5:** e00293.
3 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054–62.
4 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. *J Crit Care* 2020; published online March 10. DOI:10.1016/j.jcrc.2020.03.005.
5 Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020; published online March 9. DOI:10.1093/cid/ciaa237.

Hydroxychloroquine prophylaxis for COVID-19 contacts in India

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More than a billion Indians currently stand at the precipice of a massive increase in cases of coronavirus disease 2019 (COVID-19). India had shown a staggered course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission, with 1397 cases diagnosed between Jan 31, and April 1, 2020. However, there has been a recent surge in cases, with numbers rising to 5194 as of April 8.[1]

The Indian Council of Medical Research, under the Ministry of Health and Family Welfare, has recommended chemoprophylaxis with hydroxychloroquine (400 mg

twice on day 1, then 400 mg once a week thereafter) for asymptomatic health-care workers treating patients with suspected or confirmed COVID-19, and for asymptomatic household contacts of confirmed cases.[2] The document states "its use in prophylaxis is derived from available evidence of benefit as treatment and supported by preclinical data". Although some in-vitro evidence supports the antiviral activity of hydroxychloroquine and its precursor chloroquine, there is no peer-reviewed publication that evaluates either drug for exposure prophylaxis of SARS-CoV-2 infection. Even for treatment of diagnosed cases, only one small study reported faster nasopharyngeal viral clearance, with no data for clinical improvement.[3] This evidence, or the lack thereof, hardly justifies state-endorsed, widespread use of hydroxychloroquine for prophylaxis.

We are deeply concerned that in this environment of global panic, an endorsement by the highest scientific body of India (and also by the President of the USA)[4] will create an overly optimistic perception of the effectiveness of hydroxychloroquine among the public. Markets in the USA are already reporting a short supply of both hydroxychloroquine and chloroquine.[4] The situation in India is no different, probably indicating widespread self-medication.

The shortage of chloroquine, an inexpensive antimalarial in low-income malaria-endemic countries like India, could lead to preventable morbidity and mortality. Moreover, mathematical models estimate a worst-case scenario of 10 million cases of COVID-19 in New Delhi, India, alone in the coming weeks.[5] In these chaotic times, no health-care system can screen such a large number of healthy contacts for concomitant QTc prolonging medicines, long QT syndromes, or glucose-6-phosphate dehydrogenase deficiency. Even a 0·1% proportion of serious complications would amount to more than 10 000 severe adverse events in New Delhi alone, a number an already overwhelmed health-care system would not be able to cope with. The drug is untested, the benefits unknown, and the risks not negligible, especially at this scale of use. Moreover, the safety of these immunomodulators in people at risk of a severe viral illness has never been evaluated.

An ongoing pandemic justifies leeway in generation and interpretation of evidence in the interest of public health. However, all scientific reasoning cannot be abandoned citing desperate times. A blanket recommendation for chemoprophylaxis in the absence of credible evidence might be contentious to say the least. If hydroxychloroquine is to be used, a clear informed choice needs to be offered to every contact, explaining the scarcity of evidence for its efficacy and its potential risks. Additionally, all outcome events should be recorded. If this is not done, the risk–benefit assessment would be skewed, adverse events accepted as collateral damage, and a drug accepted provisionally in a time of crisis could become commonplace as standard of care for a long time to come.

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1 Our World in Data. Total and daily confirmed COVID-19 cases, India. 2020. https://ourworldindata.org/grapher/total-and-daily-cases-covid-19?country=IND (accessed April 8, 2020).
2 National Taskforce for COVID-19. Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. 2020. https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf (accessed March 23, 2020).
3 Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; 2020; published online March 20. DOI:10.1016/j.ijantimicag.2020.105949.
4 Marchione M. "Game changer"? Trump-touted malaria drugs spur hope, shortages. March 23, 2020. https://www.washingtontimes.com/news/2020/mar/23/chloroquine-and-hydroxychloroquine-donald-trump-to (accessed March 24, 2020).
5 Mandal S, Bhatnagar T, Arinaminpathy N, et al. Prudent public health intervention strategies to control the coronavirus disease 2019 transmission in India: a mathematical model-based approach. *Indian J Med Res* 2020; published online March 23. DOI:10.4103/ijmr.IJMR_504_20.

Hydroxychloroquine prophylaxis for high-risk COVID-19 contacts in India: a prudent approach

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We read with interest the Correspondence from Sahaj Rathi and colleagues[1] on hydroxychloroquine prophylaxis for COVID-19 contacts in India. The authors see the decision by the Indian Council of Medical Research, under the Ministry of Health and Family Welfare, to recommend chemoprophylaxis with hydroxychloroquine in select groups of contacts at high risk as an abandonment of scientific reasoning in desperate times. We present our counterview on this issue.

The safety concerns raised by Rathi and colleagues include haemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency and QTc prolongation. The prevalence of glucose-6-phosphate dehydrogenase deficiency in India ranges from 0% to 10%, with heterogenous distribution and incomplete penetrance.[2] Haemolysis is not clinically significant when hydroxychloroquine is administered in usual therapeutic doses to individuals with WHO class II and III glucose-6-phosphate dehydrogenase deficiency, and the safety of hydroxychloroquine is well established