coronavirus-drug-remdesivir-during-clinical-trial/ar-BB13ui2k
50. Canadian Agency for Drugs and Technologies in Health. Remdesivir. Updated 2020 Apr 20 [cited 2020 May 23]. Available from: https://covid.cadth.ca/treatment/remdesivir/
51. Rajagopal D. WHO calls halt to solidarity trial of HCQ. *Economic Times*. 2020 May 26 [cited 2020 Jun 2]. Available from: https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/who-calls-halt-to-solidarity-trial-of-hcq/articleshow/75990966.cms?from=mdr
52. Chitguppi R. Lancet faces severe criticism from scientific community: Hydroxychloroquine study is hiding data. *Dental Tribune*, South Asia edition. 2020 May 30 [cited 2020 Jun 2]. Available from: https://in.dental-tribune.com/news/lancet-faces-severe-criticism-from-scientific-community-hydroxychloroquine-study-is-hiding-data/
53. Mehra MR, Ruschitzka F, Patel AN. Retraction - Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis [retraction of: Lancet. 2020 May 22;]. *Lancet*. 2020 Jun 5[cited 2020 Jun 10]; S0140-6736(20)31324-6. doi:10.1016/S0140-6736(20)31324-6. Online ahead of print.
54. ANI. ICMR writes to WHO, says international HCQ trial dosages four times higher than Indian trials. 2020 May 29 [cited 2020 Jun 2]. Available from: https://www.timesnownews.com/health/article/icmr-writes-to-who-says-international-hcq-trial-dosages-four-times-higher-than-indian-trials/598726
55. Randomised Evaluation of COVID-19 Therapy (RECOVERY). Recruitment to the RECOVERY Trial continues as planned. 2020 May 26 [cited 2020 Jun 2]. Available from: https://www.recoverytrial.net/news/recruitment-to-the-recovery-trial-continues-as-planned
56. Mishra M, Maddipatla M. Reuters. Gilead ties up with generic drugmakers for COVID-19 drug supply. *Reuters*. 2020 May 12 [cited 2020 Jun 2]. Available from: https://in.reuters.com/article/us-health-coronavirus-gilead-sciences/gilead-ties-up-with-generic-drugmakers-for-covid-19-drug-supply-idINKBN22O2HJ
57. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - Preliminary report. *N Engl J Med*. 2020 May 22;10.1056/NEJMoa2007764. Epub ahead of print.
58. *Business Wire*. Gilead announces results from phase 3 trial of Remdesivir in patients with moderate COVID-19. Businesswire.com. 2020 Jun 1[cited 2020 Jun 2]. Available from: https://www.businesswire.com/news/home/20200601005310/en/
59. Institute for Clinical and Economic Review. Alternative pricing models for Remdesivir as a Treatment for COVID-19. 2020 May1 [cited 2020 May 7]. Available from: https://icer-review.org/announcements/alternative_pricing_models_for_remdesivir/
60. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020 Apr 1;3(4):e208857.
61. US Food and Drug Administration. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. 2020 Apr 24[cited May 7]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

Covid-19 chemoprophylaxis: Ethics of prevention based on anecdotal evidence

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Abstract

The ongoing pandemic of Covid-19 caused by the SARS-CoV-2 virus has infected more than 6 million all over the world and has caused more than 3.8 lakh fatalities till date. Health workers are the frontline responders and are exposed to a plethora of health hazards. Recently, an advisory by the Indian Council of Medical Research for the use of hydroxychloroquine as post-exposure prophylaxis was hailed as an outstanding initiative for the protection of healthcare workers and high risk contacts of patients. But the evidence of effectiveness available is only from in vitro studies and non-randomised control trials of insufficient sample size. Several ongoing large scale clinical trials are focused on the same research questions, the preliminary results of which are still awaited. The present study discusses the ethics of the introduction of therapeutic or preventive interventions based on limited available evidence during the ongoing pandemic of Covid-19.

Keywords: *Covid-19, chemoprophylaxis, hydroxychloroquine, cardiovascular disease, co-morbidities, ICMR*

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Introduction

The ongoing pandemic of Covid-19 caused by the SARS-CoV-2 virus has infected more than 6 million all over the world, and has caused more than 3.8 lakh fatalities till date (1). Health workers, including doctors, nurses, laboratory personnel and other support staff are the frontline responders and face hazards such as pathogen exposure, long working hours, psychological distress, fatigue, occupational burnout, stigma and physical and psychological violence (2). Initial data from Wuhan in China, the earliest hotspot, indicates that the risk of infection among health workers is thrice that among the general population. Infection prevention and control (IPC) and appropriate personal protective equipment (PPE) has been proven to be effective in prevention of infection among

health workers (2). An advisory issued by the Indian Council of Medical Research (ICMR) for the use of hydroxychloroquine (HCQ) as post-exposure prophylaxis was hailed as an outstanding initiative for the protection of health workers. The advisory also contains a caveat not to have a false sense of security with intake of the medication (3). Nevertheless, there has been a surge in demand for HCQ among the general population.

Hydroxychloroquine and Covid-19

The history of HCQ dates back to the use of cinchona tree bark for malaria by the Peruvian people in the 1600s, followed by extraction of quinine from the bark by French chemists in 18th century Europe. In earlier days, quinine was used extensively among soldiers in the American Civil War and World War I. During World War II, German scientists first started trials of the quinine derivative chloroquine against malaria. The hydroxylated version of chloroquine was synthesised in 1959 to reduce the adverse effects of chloroquine. Like chloroquine, HCQ also had lisosomotropic properties (4). HCQ is also used in chronic inflammatory diseases like systemic lupus erythematosus (SLE) and rheumatoid arthritis Both chloroquine and HCQ have been found to block viral entry into cells by inhibiting glycosylation of host cell receptors, proteolytic processing, and endosomal acidification. Both the agents also have immunomodulatory properties. In vitro studies has have shown that both chloroquine and HCQ are effective in inhibiting SARS-CoV-2, the virus causing Covid-19 (5).

Evidence of effectiveness

Evidence of novel interventions being effective is usually collected and accepted through large-scale randomised control trials. The importance of comparison between treatments and control groups cannot be underestimated as this is a vital and preliminary step before accepting the effectiveness of a preventive or therapeutic agent (6). Though hydroxychloroquine has been in use previously in various immunological disorders like SLE (7), its use for chemoprophylaxis of Covid-19 is a part of novel intervention, which warrants extensive trial-based evidence generation before being used on a large scale. Otherwise, there will be no clarity on the benefits and risks associated with the intervention.

The evidence available for use of HCQ as a chemoprophylactic drug are as follows:

- Gao et al, in a letter to the editor (8), conveyed a news briefing by the State Council of China of February 17, 2020, which indicated marked efficacy and acceptable safety of chloroquine phosphate in treating Covid-19 pneumonia in multicentre clinical trials conducted in China. The authors said initial results from more than 100 patients had demonstrated that chloroquine phosphate is superior to a control treatment in inhibiting the exacerbations of pneumonia and improving lung imagery findings, promoting negative virus conversion of cases, and shortening the course of the HCQ disease. Severe adverse events were not noted among these patients (8). In terms of evidence generation regarding, this could not add any value because of poor quality of the evidence. The authors conveyed the urgency of evidence creation through clinical trials which can prove vital in the management of Covid-19.
- Mitjà et al reported, through a correspondence, ongoing clinical trials for assessment of HCQ which were under way in China (9). They conveyed that the first clinical trial (NCT04261517) had shown positive preliminary outcomes, but that this could not be accepted as conclusive because of a small sample size. A multicentre randomised control trial was also being planned to assess the efficacy of antivirals, preventive efficacy of HCQ against SARS-CoV-2 (9). The authors conveyed the prospects of ongoing trials regarding the prophylactic role of hydroxychloroquine. They emphasised the need for larger clinical trials with bigger sample sizes to have conclusive evidence. The use of HCQ as a prophylactic has already been initiated in India.
- Wang et al, in a letter to the editor (10), concluded that remdesivir and chloroquine are highly effective in controlling the 2019-nCoV infection in vitro. In this study, the antiviral efficiency of seven approved drugs (ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir and favipiravir) were tested against SARS-CoV-2 in Vero E6 cells. The researchers concluded that two compounds, remdesivir and chloroquine, potently blocked the virus at low micromolar concentration and showed a high selectivity index. According to the time of addition assay conducted simultaneously, chloroquine, which is widely used against malaria and autoimmune disease, works both during entry and post-entry levels of virus infection in Vero e6 cells. Remdesivir was shown to function at a stage post virus entry. The authors also concluded that the effective dose of chloroquine is clinically achievable (10). This study provides convincing evidence of in vitro effectiveness of remdesivir and chloroquine against SARS-CoV-2. As this was an in vitro study, the results have to be replicated through larger clinical trials before being used clinically.
- Yao et al assessed the in vitro activity of HCQ against SARS-CoV-2 in infected Vero cells and concluded that HCQ (EC50=0.72μM) was more potent than chloroquine (EC50=5.47μM) in vitro, both as treatment and prophylaxis. They used a physiologically-based pharmacokinetic model and concluded that the loading dose of 400 mg hydroxychloroquine twice daily, followed by 200 mg twice daily for four days reached three times more potency, as compared to 500 mg twice daily dosing for five days of chloroquine phosphate (11). This study reinforces the evidence of in vitro effectiveness of chloroquine and its derivative HCQ against the SARS-CoV-2 virus. The authors also proposed a model-based dosing regimen for HCQ, which can serve as an important dosing option for clinical trials before being conclusively proven.

- One of the most discussed studies was that carried out in Marseilles, France, by Gautret et al to assess the therapeutic efficacy of HCQ and azithromycin. It was a non-randomised, open label trial, involving 36 patients. Hospitalised patients more than 12 years of age, with PCR documented SARS-CoV-2 positivity, were included in the study. Patients with retinopathy, G6 PD deficiency and QT prolongation, pregnant and nursing mothers were excluded. Based on the expected efficacy of 50%, the sample size was calculated as 48, but only 42 could be included after implementing the inclusion criteria. Six patients were lost to follow-up within six days of medication, hence the final analysis included 36 patients (20 in the treatment group, and 16 in the control group). The treatment group (N=20) was given HCQ 200 mg three times per day for 10 days. Fourteen of those in the treatment group were given HCQ only, and six were given an HCQ and azithromycin combination. The results showed a significant reduction of viral carriage among the treatment group on day 6 post inclusion, as compared to the control group, and a much lower average carrying duration than reported among the untreated patients. The addition of azithromycin for six patients was significantly more efficient for virus elimination from day 3 onwards (12). This was a very significant study, where, for the first time, the authors used a control group for comparison of the effectiveness of HCQ. The outcome indicators used are also well accepted. However, the study was non-randomised, the sample size was insufficient and they were unable to include the calculated number of patients. The comparison population was insufficient with less than 1: 1 ratio between the treatment and comparison groups. Confounders were not taken into consideration either during sampling or the stage of analysis. Concerns regarding the inclusion criteria and method of triage have been raised by the International Society of Antimicrobial Chemotherapy (13).
- Gautret et al also carried out a subsequent observational pilot study (14) to assess the clinical and microbiological effects of the combination of HCQ and azithromycin. Eighty patients (including those in the earlier study) were included and followed up for at least six days. The median age of the population was 52.5 years and 53.8% of them had at least one comorbidity. Patients were given HCQ (200 mg three times daily for 10 days) and azithromycin (500 mg on day1 and 250 mg once daily for four days), after assessment of all contraindications. The average time between hospitalisation and onset of symptoms was five days. On admission, 5% were asymptomatic, 41% had upper respiratory tract infection, 54% had lower respiratory tract infection, and only 15% had fever on presentation. 92% of the patients had low early warning scores (NEWS score). After five days of treatment 81.2% of the patients were discharged and 15% needed oxygen therapy. Mean number days of treatment from initiation to discharge was 4.1 days. A rapid fall of nasopharyngeal viral load was seen among the patients, 83% of them tested negative on day 7, and 93% by day 8 (14). The study had a significantly larger sample size than the previous study. The inclusion criteria and precautions taken before administration of HCQ were convincing as regards safe and ethical practice. As the study was a pilot study with an observational design, it can only help in forming a hypothesis of effectiveness of HCQ against SARS-CoV-2. However, it has to be proved through interventional studies before being used in clinical practice.

Evidence in the time of Covid-19

With the ever increasing number of Covid-19 patients in the intensive care units, the pandemic has created an urgent need for effective therapeutic agents for treatment. However, in such times of despair, there is a strong chance that even the weakest available evidence may be used as the best available treatment option. It might seem helpful in the short term, but have serious long term deleterious effects. It may also inhibit research and development of more prudent and effective solutions. Hence, there is an evident need to guard against weak evidence being used as a disease management norm without sufficient deliberation

The following issues entail cautious consideration of the available data with regard to the use of HCQ as chemoprophylaxis in India, and elsewhere:

1. Molina et al studied the clinical benefits of a combination of hydroxychloroquine and azithromycin in 11 consecutively selected patients with severe Covid-19 infection. The researchers had followed the dosing regimen used and recommended by Gautret et al. Within five days of starting therapy, one patient died, two patients became critically ill and were transferred to the ICU, and one patient had to discontinue treatment due to QT prolongation.. The authors concluded that the drugs (HCQ and azithromycin) revealed no efficacy in changing the virological and clinical outcome of the patients (12, 15). The study was an observational study and samples were selected consecutively without any randomisation. The sample size was also insufficient to provide any conclusive hypothesis. This study was an effort to replicate the results by Gautret et al and was not successful in doing so.

2. A pilot study by Jun et al in China assessed the effectiveness of HCQ in the treatment of Covid-19. The study included 30 diagnosed patients of Covid-19, randomised into two groups of 1: 1 ratio each. While the treatment group was given conventional therapy and HCQ; the control group was given conventional treatment. The dose of HCQ was 400 mg per day for five days for the treatment group. Nasopharyngeal viral conversion of the two groups was compared on day 7. The results revealed no significant difference of viral shedding in the nasopharyngeal swabs or clinical outcomes of the two groups on day 7 (16). The study being a pilot randomised control trial with a very small sample size, the results were inconclusive on the effects of HCQ use in a clinical trial scenario.

3. An observational study, with the largest sample size till date to assess the association of HCQ use and intubation/ death among Covid-19 patients, was carried out by Geleris et al (17). Of the initial 1446 patients consecutively included in the study, 1376 patients were finally included in analysis, after excluding 70 patients due to critical health or death or discharge within 24 hours of inclusion. Among these, 811 (58.6%) were started on HCQ (600 mg twice daily on day1 and 400 mg daily for five days). Patients treated with HCQ were more severely ill at presentation than those not treated with HCQ. The final analysis did not reveal any statistically significant association of hydroxychloroquine and primary end points (intubation/ death) (17). The researchers strongly recommended clinical trials to verify the findings

4. A retrospective multicentre cohort study was carried out by Rosenberg et al in New York on 1438 patients to assess the association of treatment with HCQ or azithromycin with in-hospital mortality (18). The probability of death among patients receiving an HCQ and azithromycin combination was 25.7%, 19.9% among those receiving HCQ alone, 10.0% among those receiving azithromycin alone, and 12.7% among patients taking neither of the two drugs. The authors concluded, there was no significant difference of mortality among patients taking both the drugs (HCQ+ azithromycin) or HCQ/azithromycin alone as compared to patients taking neither of the two drugs. The chances of cardiac arrest among patients taking both the drugs (HCQ+ azithromycin) was significantly higher than among patients taking neither of the two drugs (18). The study included a reasonably large sample size to reinforce the inconclusiveness of HCQ therapy among Covid-19 patients.

5. Mahevas et al did a comparative observational study in four tertiary care centres in France (19), of 181 patients aged 18-80 years with documented Covid-19 pneumonia, requiring oxygen but not in intensive care, to assess the clinical efficacy of HCQ. They concluded the survival rate without transfer to ICU at day 21among the treatment group (receiving 600 mg/day of HCQ within 48 hours of admission) was 76% as compared to 75% among the control group. Overall survival rate at day 21 was 89% among the treatment group, compared to 91% among the control group.(19)survival without acute respiratory distress syndrome, weaning from oxygen, and discharge from hospital to home or rehabilitation (all at day 21. This study weakened the prospects of hydroxychloroquine further for use as a successful therapeutic agent against Covid-19 disease.

6. The Solidarity trial is a multinational trial carried out under the aegis of the WHO to find effective therapeutic interventions against Covid-19. Due to concerns raised about the safety of the drug in March 2020, the WHO had temporarily paused the HCQ arm of the Solidarity trial till the safety of the drug was reviewed by its Data Safety and Monitoring Committee (20). Subsequently, on June 3, 2020, WHO decided to continue all arms of the trial, including hydroxychloroquine, based on the available mortality data.

7. The research data regarding effectiveness of hydroxychloroquine needs to be interpreted with caution as there are precedents of in vitro effectiveness of HCQ against chikungunya, dengue, HIV and influenza, which did not translate into in vivo efficacy and clinical practice (21-23).

8. Lopinavir and ritonavir are protease inhibitors used in the management of HIV. The lopinavir – ritonavir combination was shown to be effective in in-vitro trials against SARS-CoV-2 (24). Young et al used a lopinavir-ritonavir combination in five patients in their observational study. Among these five patients, three patients had improved oxygenation. The results seemed to suggest an advantage in using this combination on Covid-19 patients (25). Subsequently, a clinical trial by Cao et al regarding the combined use of lopinavir and ritonavir in the management of Covid-19 patients revealed that there was no significant difference in clinical outcome or mortality between the treatment and control groups on day 28 of follow up (26).

Ethical fallout of ICMR advisory

The ICMR issued an advisory regarding limited use of hydroxychloroquine among health professionals and high risk contacts of Covid-19 patients (3). This was, in all probability, a well-intentioned step meant for safeguarding the health of frontline health workers.

At the same time it has several ethical fall outs which may seriously impact the health and safety of the population in future. These are

- There was no mention of any quoted reference for available evidence based on which the advisory was developed and released. Even though there may be convincing preliminary results of some ongoing trial, it could have been cited as a part of an authentic health communication to health workers, especially doctors around the country.
- Specific exclusions/ contraindications for the prophylactic use mentioned in the advisory were children under 15 years of age, known cases of retinopathy and known hypersensitivity to HCQ or 4-aminoquinoline compounds. The proven and potentially life threatening side effect of drug-induced QT interval prolongation, acute hypoglycaemia could have been included along with guidance to assess risk benefit before administration of HCQ (27, 28).
- A study by Shankar et al has shown that around 60% of the physicians in India are overweight and 10% of them are taking diabetic medication (29). Hegde et al showed that 50% of the doctors they studied were at high general risk for cardio vascular disease (CVD) (30). The incidence of CVD is 12 -16% in India (31). This implies that there may be a sizable population of physicians and high risk exposures,

who would consider taking chemoprophylaxis in the belief that Covid-19 prevention outweighs the risks associated with the medication.

- More details regarding life-threatening drug interactions of other coadministered drugs along with specific initial preventive evaluation, eg cardiac evaluation before taking the drug, could have been included in the advisory instead of blanket consultation with a physician.
- The didactic recommendation of "Chemoprophylaxis should not instil a sense of false security" does not serve the purpose, as the very advisory without any documented or cited evidence could be the reason for a false sense of security.
- There is no mention in the advisory regarding the duration of its protection and if a repeat dose is useful, and specifying the schedule of such a repeat dose if ever needed. . The pandemic is presumed to stay at least six months in a community (32), and the prescribed dose of HCQ is only effective for two months. Hence, there is a need for information and clarity on the further course and schedule of HCQ use after the currently prescribed two months of treatment.

Recent evidence from ICMR

On May 31, more than two months after the ICMR advisory on HCQ prophylaxis was issued, Chatterjee et al published a case control study assessing the factors responsible for SARS-CoV-2 infection (33). They included a case group of 378 (symptomatic and diagnosed as Covid-19 positive) and a control group of 373 (symptomatic but Covid-19 negative). They concluded that only a loading dose of HCQ (400mg taken twice on day 1) followed by two to three maintenance doses(400 mg weekly) seems to increase the chances of infection(to almost double) but the protective efficacy is significantly higher after four maintenance doses (as high as 80%). This is an observational study. The authors included patients through interview over phone and collected data of their self-declared dosing of HCQ along with self-reported adverse events (33). This study is the first to indicate prophylactic efficacy of HCQ among health workers against SARS-CoV-2. This has to be replicated elsewhere with larger observational studies or clinical trials before being accepted for wider implementation.

Conclusion

The Covid-19 pandemic may be one of the biggest threats to human existence in the last hundred years. Efforts are underway all over the world for control of this pandemic through research and development. However, this should not undermine the basic ethical and scientific principles of research, and calls for taking ethical, prudent and evidence based decisions which can have a long lasting positive impact on public health. The pandemic necessitates enormous research efforts for the production of novel therapeutics or preventive vaccines. While bureaucratic red tape can be reduced to hasten research output, research still has to go through its gradual evidence generation process from preclinical trials and observational studies to large multi-centric clinical trials before being accepted.

Hydroxychloroquine use as a repurposed therapeutic or prophylactic agent in Covid-19 patients should wait till preliminary evidence in the form of randomised control trials can support its use. Preclinical and observational studies should only be used for generation of hypotheses for clinical trials. Till then, the use of such drugs should be limited to participants of trials, while protecting their legal and ethical rights. Till such time as a novel therapeutic agent is established, non-pharmacological measures like the use of masks or PPE, hand washing and social distancing should be pursued vigorously for the prevention of Covid-19.

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References

1. World Health Organization. Coronavirus disease (COVID-19) Situation Dashboard. [cited 2020 Apr 1]. Available from: https://covid19.who.int/
2. World Health Organization. Coronavirus disease (COVID-19) outbreak: rights,roles and responsibilities of health workers, including key considerations for occupational safety and health. Interim guidance. 2020 Mar 19 [cited 2020 Apr 1]. Available from: https://www.who.int/publications-detail/coronavirus-disease-(covid-19)-outbreak-rights-roles-and-responsibilities-of-health-workers-including-key-considerations-for-occupational-safety-and-health
3. Indian Council of Medical Research. Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. New Delhi: ICMR; 2020 Mar 22[cited 2020 Apr 1]. Available from: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf
4. Solitro AR, Mackeigan JP. Leaving the lysosome behind: Novel developments in autophagy inhibition. *Future Med Chem*. 2016 Jan;8(1):73–86.
5. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A Review. *JAMA*. 2020Apr 13. doi: 10.1001/jama.2020.6019. Epub ahead of print.
6. Celentano D, Szklo M. Assessing preventive and therapeutic measures: Randomized trials. In: *Gordis Epidemiology*. 6th ed.. Philadelphia: Elsevier; 2019.
7. Jameson J, Fauci A, Kasper D, Hauser S. Harrison's Principles of Internal Medicine. 20th ed. New Delhi: Mc GrawHill companies; 2018.
8. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020 Mar 16;14(1):72–3.
9. Mitjà O, Clotet B. Correspondence: Use of antiviral drugs to reduce COVID-19 transmission. *Lancet Glob Heal*. 2020 Mar 19[cited 2020 Apr 4];http://dx.doi.org/10.1016/S2214-109X(20)30114-5. Epub ahead of print.
10. 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 Res*. 2020 Mar;30(3):269–71.
11. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome. *Clin Infect Dis.* 2020 Mar 9; ciaa237. Available from: https://pubmed.ncbi.nlm.nih.gov/32150618
12. 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. *Int J Antimicrob Agents*. 2020 Mar 20 [cited 2020 Apr 2];105949.Epub ahead of print. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32205204
13. International Society of Antimicrobial Chemotherapy. Statement on IJAA paper. 2020 Apr 3[cited 2020 May 11]. Available from: https://www.isac.world/news-and-publications/official-isac-statement
14. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and

azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis*. 2020 Mar-Apr;34:101663. Epub 2020 Apr 11.
15. Molina JM, Delaugerre C, Goff J Le, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Médecine Mal Infect*. 2020 Jun; 50(4): 384. Epub 2020 Mar 30 [cited 2020 Apr 2]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0399077X20300858
16. Jun C, Danping L, Li L, Ping L, Qingnian X, Lu X, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ* (Medical Sci). 2020 May 25;49(2):215-19. [Chinese]
17. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* 2020 May 7 [cited 2020 May 11];NEJMoa2012410. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2012410
18. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA*. 2020 May 11[cited 2020 Jun 1]; e208630. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32392282
19. Mahévas M, Tran V-T, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020 May 14 [cited 2020 May 18];369:m1844. Available from: http://www.bmj.com/lookup/doi/10.1136/bmj.m1844
20. World Health Organization."Solidarity" clinical trial for COVID-19 treatments. 2020 Jun 3[cited 2020 Jun 5]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
21. Roques P, Thiberville SD, Dupuis-Maguiraga L, Lum FM, Labadie K, Martinon F, et al. Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. *Viruses*. 2018 May 17 [cited 2020 Apr 2];10(5).268. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29772762
22. Paton NI, Lee L, Xu Y, Ooi EE, Cheung YB, Archuleta S, et al. Chloroquine for influenza prevention: A randomised, double-blind, placebo controlled trial. *Lancet Infect Dis*. 2011 May 5;11(9):677–83.
23. Paton NI, Goodall RL, Dunn DT, Franzen S, Collaco-Moraes Y, Gazzard BG, et al. Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: A randomized controlled trial. *JAMA*. 2012 Jul 25 [cited 2020 Apr 2];308(4):353–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22820788
24. Choy KT, Wong AYL, Kaewpreedee P, Sia SF, Chen D, Hui KPY, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res*. 2020 Jun 1;178:104786.
25. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected with SARS-CoV-2 in Singapore. JAMA. 2020 Apr 21;323(15):1488–94.
26. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32187464
27. WHO Evidence Review Group. The cardiotoxicity of antimalarials. Geneva: WHO-ERG;2016 Oct13–4 [cited 2020 Apr 2]. Available from: http://www.who.int/malaria/mpac/mpac-mar2017-erg-cardiotoxicity-report-session2.pdf
28. Hydroxychloroquine: Drug information.*UpToDate*. Date unknown[cited 2020 Apr 3]. Available from:https://www.uptodate.com/contents/hydroxychloroquine-drug-information?source=autocomplete&index=0~1&search=hydr#F180902
29. Shankar SP, Uma Sudhan E, Reddy KHV, Singh R, Ramya N. Prevalence of obesity and diabetes among health care physicians in Pondicherry, India. *Int J Adv Med.* 2019 May 24;6(3):646.
30. Hegde SK, Vijayakrishnan G, Sasankh A, Venkateswaran S, Parasuraman G. Lifestyle-associated risk for cardiovascular diseases among doctors and nurses working in a medical college hospital in Tamil Nadu, India. *J Family Med Prim Care.* 2016 Apr-Jun;5(2):281-5.
31. Nag T, Ghosh A. Cardiovascular disease risk factors in Asian Indian population: A systematic review. *J Cardiovasc Dis Res*. 2013 Dec;4(4): 222-8. 29.
32. Danon L, Brooks-Pollock E, Bailey M, Keeling MJ. A spatial model of CoVID-19 transmission in England and Wales: early spread and peak timing. *medRxiv*. 2020 Feb 14 [cited 2020 Apr 3]; doi:10.1101/2020.02.12.20022566. Available from: https://www.medrxiv.org/content/10.1101/2020.02.12.20022566v1
33. Chatterjee P, Anand T, Singh K, Rasaily R, Singh R. Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. *Indian J Med Res.* 2020 May 28 [cited 2020 Jun1];DOI: 10.4103/ijmr.IJMR_2234_20 Epub ahead of print. Available from: http://www.ijmr.org.in/preprintarticle.asp?id=285520

"Slow research" in the time of Covid-19

SHUBHA RANGANATHAN

Abstract

This commentary reflects on what it means to do public health and social science research in a post-Covid world. Given the global urgency brought on by the pandemic, it appears as if any kind of non-Covid research has become redundant or meaningless. Yet, in many ways, the pandemic has highlighted the need to go back to many of the old lessons in the social sciences and public health. Here, I draw on the concept of "slow research" in global health to foreground some of these principles – the need to pay attention to local contexts and particularities, the importance of time to contemplate on the complexity of findings, and the need to think beyond global agendas that seek quick findings and globally scalable solutions, and focus on what is socially relevant in different local contexts. While not cast in opposition to rapid research, slow research is an important alternative, particularly in pandemic times.

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What does it mean to do public health and social science research in a post-Covid world? How do we understand what