

## Original Research Article

# Did hydroxychloroquine played crucial role as prophylactic drug against SARS-CoV-2 infection in resource-constrained and overloaded health care systems in countries like India: a prospective multicentre study in dedicated COVID hospitals

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### ABSTRACT

**Background:** The Indian council medical research (ICMR) recommended to use hydroxychloroquine (HCQ) as a prophylactic agent against Severe acute respiratory syndrome coronavirus-2019 (SARS-COV-2) infection to cater need to protect high-risk individuals considering its pre-clinical data. This study explores role of HCQ in health care workers serving in coronavirus-2019 (COVID-19) pandemic.

**Methods:** The study was planned as multi center observational study, conducted from April, 2020 to August 2020 at COVID-19 hospitals in India. HCQ 400 mg twice a day on day-1 followed by 400 mg once weekly for next 7 weeks was administered to Health care workers (HCW). RTPCR test was conducted at 3 months post last dose of prophylaxis in symptomatic health care workers. IgG test was conducted in all participants at 3 months.

**Results:** We enrolled 1310 asymptomatic frontline healthcare workers, of which 585 (45%) were male and 725 (55%) were female. Chi-Square test statistical analysis in RTPCR Test showed  $p=0.515$ ,  $p=0.634$ ,  $p=0.00$  in doctor and nurse, housekeeping and other staff respectively. Chi-Square test statistical analysis in IgG antibody tests showed  $p=0.305$ ,  $p=0.449$  and  $p=0.345$  in doctor and Nurse, Housekeeping and Other staff respectively.

**Conclusions:** HCQ did not provide statistically significant pre exposure prophylaxis to doctors, nurses and housekeeping staff. However for, "other staff members category" it showed highly statistically significant prophylaxis effect with respect to RTPCR positive test results in comparison with HCW who did not consume HCQ prophylaxis. And hence HCQ could certainly play a crucial role in resource-constrained and overloaded health care systems in countries like India.

**Keywords:** Hydroxychloroquine, SARS-COV-2 infection, Health care workers, COVID-19, IgG seroprevalence

### INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a positive RNA virus in the coronaviridae family, which caused coronavirus-2019 (COVID-19)

disease since then, the disease has spread unprecedentedly, and on March 11, 2020, the World Health Organization (WHO) declared it a "global pandemic".<sup>1</sup> There is currently no effective prophylactic drug available for this disease.<sup>2</sup>

Although many trials are underway to treat COVID-19, there is still a lack of scientific research on chemoprophylaxis, which has the potential to flatten the curve so as to get more time to complete research on vaccines.<sup>1</sup>

The use of Chloroquine (CQ) as an aspirin drug for influenza virus already exists. CQ and its derivative hydroxychloroquine (HCQ) were already used successfully in mouse models, and in the case of coronavirus for SARS-COV, which shows strong antiviral properties in vitro.

The Indian Council Medical Research (ICMR) recommended to use HCQ as a prophylactic agent against SARS-COV-2 infection to cater need to protect high-risk individuals considering its pre-clinical data.<sup>3</sup> Prior to this pandemic, more than 100 broad-spectrum antivirals (BSAs) had already been identified which have shown action against 78 viruses. It is known to prevent the virus from entering host cells and its prophylaxis use is also supported by preclinical data.<sup>4</sup>

Chloroquine is effective, inexpensive and safe drug, it is used to treat a number of human diseases, including malaria, amoebiasis, and human immunodeficiency viruses, and is effective in preventing the spread of SARS COV in cell cultures.

In March 2020, the Indian Council of Medical Research (ICMR) recommended the use of HCQ (400 mg twice a day, 400 mg once a week that after for 7 weeks) for prophylaxis against COVID-19.<sup>5</sup>

Objective of the study is to evaluate the use of hydroxy chloroquine for prophylaxis of SARS-CoV-2 infection in, "health care workers".

## **METHODS**

### **Study design**

The study was planned as multi center open-label, observational study. It was conducted between April, 2020 and August 2020 at a dedicated COVID-19 hospital in India. Study is conducted at Bhaktivedanta Hospital and Research Institute situated at Mira Road, Thane, Maharashtra and Sheth P V Doshi Hospital situated at Mira Road, Thane, Maharashtra.

Bhaktivedanta Hospital Ethics Committee for Biomedical and Health Research, is Government of India accredited committee, which approved the research protocol and subsequent amendments.

### **Inclusion criteria**

Asymptomatic health care workers 18 years onwards, all genders. Health care workers who are working atleast 4

days a week (minimum 5-6 hours work per day) in COVID designated wards and ICU were considered for the study.

### **Exclusion criteria**

Known cases of retinopathy, known hypersensitivity to hydroxychloroquine, 4 aminoquinoline compounds and significant cardiovascular disease. Data validation, cleaning and statistical analysis are done by expert research associates.

### **Procedures**

As per ICMR recommendation hydroxy chloroquine was offered on the prescription of registered medical practitioner. Physician interviewed participants to review for any adverse event or potential drug interaction before administration initiation of HCQ. Written informed consent was obtained from every participant. The participants were given choice to avail the hydroxychloroquine prophylaxis regimen arranged by hospital administration for health care workers.

Prophylactic use of hydroxy chloroquine was coupled with the pharmaco-vigilance for adverse drug reaction through self reporting using the pharmacovigilance program of India." A dedicated research coordinator who had no involvement in the participant enrollment, collected required data as per protocol study procedures and adverse reporting done as per Declaration of Helsinki guidelines HCQ 400 mg twice a day on Day-1, followed by 400 mg once weekly for next 7 weeks was administered to HCW.

Health care workers were asked to report to investigators for any of the symptoms, namely fever, cough, shortness of breath or difficulty breathing, tiredness, aches, running nose, sore throat. All health care workers were followed up for 3 months post last prophylactic dose of hydroxy chloroquine.

As per manufacturer's guidelines SARS-CoV-2 IgG antibodies were tested in whole blood. SARS-CoV-2 IgG antibodies screening was also provided to HCW who did not consume HCQ, such population was considered for control arm. Research coordinator collected information from participants pertaining to demographics, type of work, history of contact with patients with diagnosed COVID-19, and symptoms of infection. Study data was processed using research electronic data capture.

### **Study endpoints**

#### **Primary endpoint**

Comparison of percentage of health care workers presenting clinical features of COVID-19 at 3 months post prophylaxis among those who consumed and who didn't consume HCQ as prophylaxis.

**Secondary endpoint**

Comparison of percentage of health care workers IgG positive status for COVID-19 at 3 months post prophylaxis among those who consumed and who didn't consume HCQ as prophylaxis.

**Statistical analysis**

This study is planned to check the effectiveness of hydroxy chloroquine as prophylaxis among health care workers for COVID-19 disease. A sample of size 1310 health care workers were analyzed. Descriptive statistical analyses were performed for the study sample. The gender is presented in percentage. Chi-square test used for statistical significance determination using the SAS software.

**Table 1: Clinical study procedures.**

S. no.	Procedure	D-1	Week-1	Week 2 to week 7	3 Months
1	Signed Informed a Consent Form	X			
2	Medical History	X			
3	Clinical Examination	X	X		X
4	Review of eligibility criteria <sup>1</sup>	X			
5	Hydroxychloroquine administration <sup>2</sup>	X	X	X	
6	IgG antibody testing at 3 months <sup>3</sup>				X
7	AE/SAE recording <sup>4</sup>	X	X	X	X
8	Telephonic interview for compliance		X	X	

AE= Adverse Event, SAE=Serious Adverse Event, 1) Eligibility criteria confirmed at D1 after informed consent procedure; 2) hydroxychloroquine administration done by registered medical practioner, 3) IgG antibody testing for covid-19 was done for all by hospital administration , in the interest of employees, 4) Adverse events (AE) were defined as any new symptoms or worsening of pre-existing symptoms and were followed until complete resolution of symptoms. Serious adverse events (SAE) were defined as per the New Drug Clinical Trials - 2019 guidelines and ICMR 2017 guidelines. SAEs were reported to the "Bhaktivedanta Hospital Ethics Committee for Biomedical and Health Research" for independent adjudication of relatedness. SAEs were graded for causality. Investigators reviewed SAE's for medical management and compensation.

**Table 2: Study population demographic and results.**

Hospital staff category	Doctor and nurse	Housekeeping	Other staff	Total	
	N (%)	N (%)	N (%)	N (%)	
<b>Hospital staff number (percentage)</b>	418 (32)	87 (7)	805 (61)	1310 (100)	
Male	65 (11)	63 (11)	457 (78)	585 (100)	
Female	353 (49)	24 (3)	348 (48)	725 (100)	
<b>RTPCR Positive for COVID-19</b>	HCQ consumed	6 (38)	5 (31)	5 (31)	16 (100)
	HCQ not consumed	5 (42)	0 (0)	7 (58)	12 (100)
<b>RTPCR Negative for COVID-19</b>	HCQ consumed	278 (27)	72 (7)	672 (66)	1022 (100)
	HCQ not consumed	129 (50)	10 (4)	121 (46)	260 (100)
<b>RTPCR Test</b>	P value	0.515	0.634	0.001	0.006
<b>IgG antibody Positive for COVID-19</b>	HCQ consumed	39 (36)	18 (17)	50 (47)	107 (100)
	HCQ not consumed	24 (77)	1 (3)	6 (20)	31 (100)
<b>IgG Antibody Negative for COVID-19</b>	HCQ consumed	245 (26)	59 (6)	627 (68)	931 (100)
	HCQ not consumed	110 (46)	9 (4)	122 (50)	241 (100)
<b>IgG Antibody</b>	P value	0.305	0.449	0.345	0.657

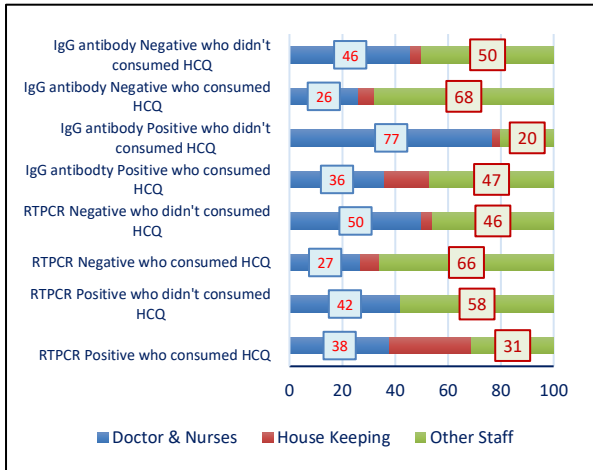
The numeric data is summarized by descriptive statistics. The gender is represented as percentage. Data was found normally distributed, checked by the Kolmogorov-Smirnov test. Chi Square test was used for statistical analysis. All testing was done at 5% (0.05) level of significance and power of 90%. Statistical analyses were done using statistical package for social sciences (SPSS) version 20.

**Role of funding source**

The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**RESULTS**

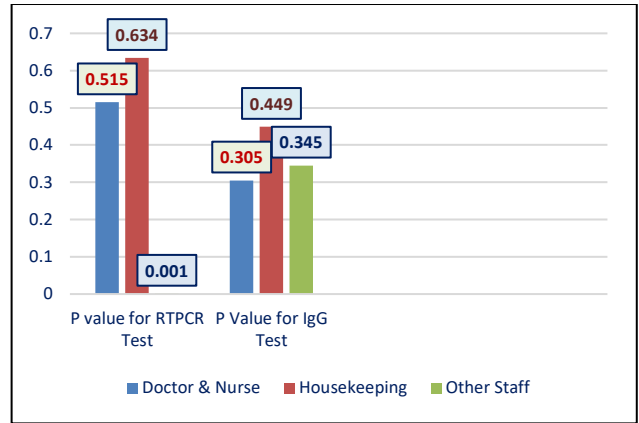
In this study we enrolled 1310 asymptomatic frontline healthcare workers. Out of which 585 (45%) were male and 725 (55%) were female. Study populace is additionally classified into three groups doctor and nurses 418 (32%) of which 65 (11%) were male and 353 (49%) were female. Housekeeping 87 (7%) of which 63 (11%) were male and 24 (3%) were female and other hospital staff 805 (61%) of which 457 (78%) were male and 348 (48%) were female (Table 2).



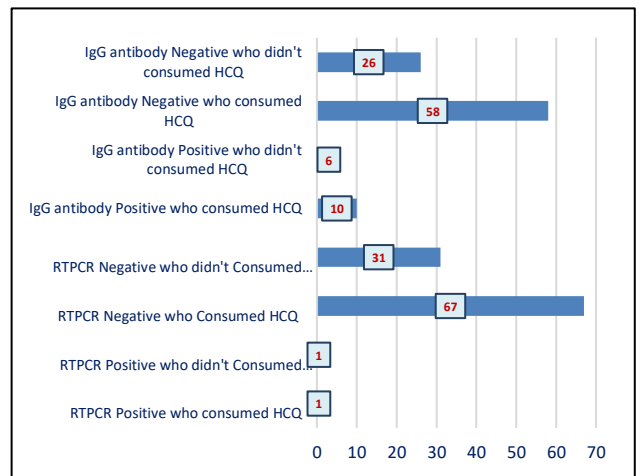
**Figure 1: Results category wise percentage.**

RTPCR was conducted at 3 months post last prophylaxis dose in symptomatic health care workers. It was found positive for COVID-19 in HCW in 6 (38%), 5 (31%) and 5 (31%) in doctor and nurse, housekeeping and other staff respectively who volunteered for administration of HCQ. And it was found positive in 5 (42%), (nil) and 7 (58%) in doctor and nurse, housekeeping and other staff respectively, who didn't volunteer for consumption of HCQ (Figure 1). It was found negative for COVID-19 in HCW in 278 (27%), 72 (7%) and 672 (66%) in doctor and nurse, housekeeping and other staff respectively who volunteered for administration of HCQ. And it was found negative in 129 (50%), 10 (4%) and 121 (46%) in doctor and nurse, housekeeping and other staff respectively who didn't volunteer for administration of HCQ (figure 1). Chi-Square test statistical analysis in RTPCR Test showed  $p=0.515$ ,  $p=0.634$ ,  $p=0.001$  in doctor and nurse, housekeeping and other staff respectively (Figure 2).

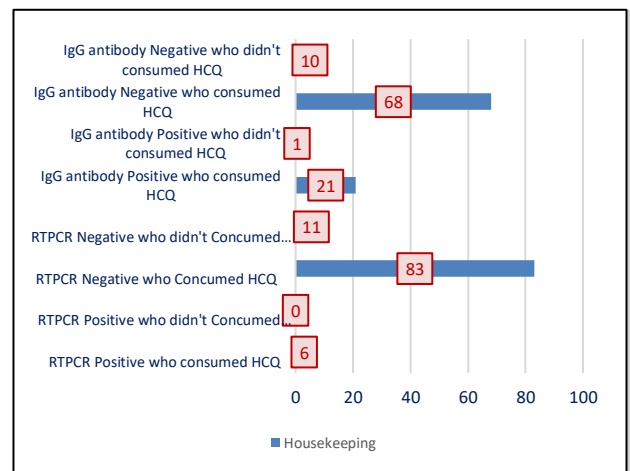
In our study who consumed HCQ as prophylaxis and found IgG antibody positive for COVID-19 were 39 (36%), 18 (17%) and 50 (47%) in doctor and nurse, housekeeping and other staff respectively. HCWs who did not consume HCQ as prophylaxis and found IgG antibody positive for COVID-19 were 24 (77%), 1 (3%) and 6 (20%) in doctor and nurse, housekeeping and other staff respectively (Figure 3,4,5).



**Figure 2: Statistical p values for RTPCR and IgG tests.**



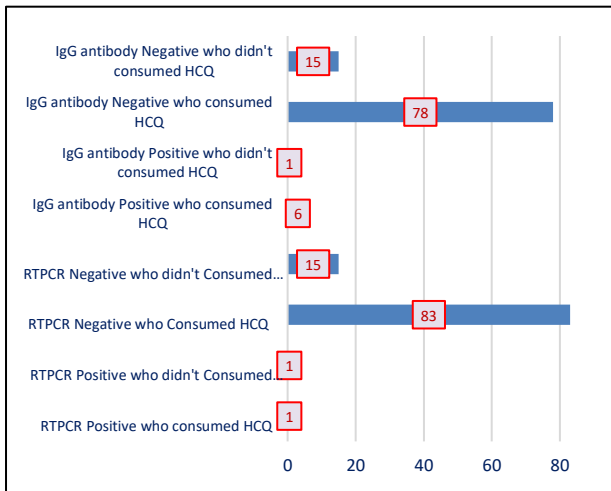
**Figure 3: Prophylaxis outcome of doctors and nurses at 3 months follow up, in percentage.**



**Figure 4: Prophylaxis outcome of "housekeeping staff" at 3 months follow up in percentage.**

Also, in our study who consumed HCQ as prophylaxis and found IgG antibody negative for COVID-19 were 245 (26%), 59 (6%) and 627 (68%) in doctor and nurse, housekeeping and other staff respectively. HCWs did not

consumed HCQ as prophylaxis and found IgG antibody negative for COVID-19 were 110 (46%), 9 (4%) and 122 (50%) in doctor and nurse, housekeeping and other staff respectively (figure 3, 4, 5). Chi-Square test statistical analysis in IgG antibody tests showed  $p=0.305$ ,  $p=0.449$  and  $p=0.345$  in doctor and nurse, housekeeping and other staff respectively (Figure 2).



**Figure 5: Prophylaxis outcome of “other staff category” at 3 months follow up in percentage.**

**DISCUSSION**

As per ICMR Guidelines dated 23rd March 2020, HCQ prophylaxis was offered to all eligible frontline health care workers (HCW).

The drug is prescribed by a registered medical professional as recommended by the ICMR. Physicians examined participants for any adverse events or possible drug interactions in the entire study duration. Prophylactic use of hydroxy chloroquine was carried out with pharmacovigilance for adverse drug reactions through self-reporting using the Pharmacovigilance Program of India.

There is healthcare system crisis around the world due to COVID-19 pandemic resulting in social and economic burden globally. Though many clinical trials are ongoing for the treatment of COVID-19, no promising medication is yet discovered. Of these, HCQ was recommended based on in vitro results showing efficacy against SARS-CO-V-2, but there is no evidence that HCQ has provided any additional clinical benefit for the treatment of hospitalized COVID-19 patients. This study attempted to study the role of HCQ in various categories of HCW.

Our study results depicted that HCQ did not provide statistically significant pre exposure prophylaxis to doctors, nurses and housekeeping staff. However for, “other staff members category” it showed very highly statistically significant prophylaxis with respect to RTPCR positive test results in comparison with HCW who did not consume HCQ prophylaxis.<sup>6</sup> One explanation could be

that prophylactic effect of HCQ was dampened in doctors and nurses due to their close proximity direct exposure while treating and caring for COVID-19 infected patients. Other staff members which includes receptionist, security personnel, administrative officers and billing staff working in COVID hospital showed highly statistically significant results are in conformity with multicentric clinical study, conducted in France, which also showed significant decrease in the viral load with the use of HCQ.<sup>7</sup>

HCQ arm to study the effectiveness of different interventions for treatment of COVID-19 was stopped in SOLIDARITY trial and RECOVERY (Randomized Evaluation of COVID-19 therapy) trial.<sup>9,10</sup> The reason for discontinuation of the trials were due to insufficient data to prove the benefit of HCQ or CQ to treat COVID-19.<sup>11</sup>

There is certain degree of immunity against SARS-CoV-2 amongst COVID-19 survivals.<sup>12</sup> It is postulated that between 60% and 80% population needs to be exposed to get herd immunity. Around 80% individuals who contracted SARS-CoV-2- are asymptomatic.<sup>13</sup> One of the important tool for surveillance of the pandemic is to check developed antibodies against SARS-CoV-2 (seroprevalence), this tool is also a indicator to predict possibility of herd immunity. The most exposed group of individuals for SARS-CoV-2 infection are certainly health-care workers and hence, one of the indicator of the spread of SARS-CoV-2 is proportion of seropositive health-care workers. In the neutralization of SARS-CoV-2, IgG antibody plays a crucial role.<sup>14</sup> And thus IgG antibody response indicates an infection as well as potential immunity.<sup>2</sup>

Seroprevalence of IgG antibodies against SARS-CoV-2 among healthcare workers who have consumed hydroxy chloroquine as prophylaxis is studied first time, to the best of our knowledge. In our study IgG seroprevalence data didn't provided statistically significant results in doctors and nurses, housekeeping and other staff category amongst those who volunteered for administration of HCQ, and who didn't volunteer for administration of HCQ. However, it is very important to note that in other staff category very highly statistically significant prophylaxis with respect to RTPCR positive test results were seen for HCW who consumed HCQ as prophylaxis in comparison with HCW who didn't consumed HCQ prophylaxis. At the same time there is no difference in IgG seroprevalence status among these. Which means that the other staff category HCW who consumed HCQ also got equally infected but weren't symptomatic, which signifies role of HCQ in curtailing the disease severity. In resource-constrained and overloaded health care systems in countries like India, HCQ could certainly play crucial role.

**Limitations of the study**

RTPCR test was conducted at 3 months post last dose of prophylaxis in only symptomatic health care workers.



Control and intervention group were not categorized by proper randomization method.

## CONCLUSION

HCQ did not provide statistically significant pre exposure prophylaxis to doctors, nurses and housekeeping staff. However for, “other staff members category” it showed highly statistically significant prophylaxis effect with respect to RTPCR positive test results in comparison with HCW who did not consume HCQ prophylaxis. And hence HCQ could certainly play a crucial role in resource-constrained and overloaded health care systems in countries like India.

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