



Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19

Pranab Chatterjee^{1, #}, Tanu Anand^{7, #}, Kh. Jitenkumar Singh², Reeta Rasaily³, Ravinder Singh⁴, Santasabuj Das⁸, Harpreet Singh⁵, Ira Praharaj⁶, Raman R. Gangakhedkar⁶, Balram Bhargava[†] & Samiran Panda⁹

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

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Background & objectives: Healthcare workers (HCWs) are at an elevated risk of contracting COVID-19. While intense occupational exposure associated with aerosol-generating procedures underlines the necessity of using personal protective equipment (PPE) by HCWs, high-transmission efficiency of the causative agent [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] could also lead to infections beyond such settings. Hydroxychloroquine (HCQ), a repurposed antimalarial drug, was empirically recommended as prophylaxis by the National COVID-19 Task Force in India to cover such added risk. Against this background, the current investigation was carried out to identify the factors associated with SARS-CoV-2 infection among HCWs in the country.

Methods: A case-control design was adopted and participants were randomly drawn from the countrywide COVID-19 testing data portal maintained by the ICMR. The test results and contact details of HCWs, diagnosed as positive (cases) or negative (controls) for SARS-CoV-2 using real-time reverse transcription-polymerase chain reaction (qRT-PCR), were available from this database. A 20-item brief-questionnaire elicited information on place of work, procedures conducted and use of PPE.

Results: Compared to controls, cases were slightly older (34.7 vs. 33.5 yr) and had more males (58 vs. 50%). In multivariate analyses, HCWs performing endotracheal intubation had higher odds of being SARS-CoV-2 infected [adjusted odds ratio (AOR): 4.33, 95% confidence interval (CI): 1.16-16.07]. Consumption of four or more maintenance doses of HCQ was associated with a significant decline in the odds of getting infected (AOR: 0.44; 95% CI: 0.22-0.88); a dose-response relationship existed between frequency of exposure to HCQ and such reductions (χ^2 for trend=48.88; $P<0.001$). In addition, the use of PPE was independently associated with the reduction in odds of getting infected with SARS-CoV-2.

[#]Equal contribution

Interpretations & conclusions: Until results of clinical trials for HCQ prophylaxis become available, this study provides actionable information for policymakers to protect HCWs at the forefront of COVID-19 response. The public health message of sustained intake of HCQ prophylaxis as well as appropriate PPE use need to be considered in conjunction with risk homeostasis operating at individual levels.

Key words Dose-response relationship - healthcare worker - hydroxychloroquine prophylaxis - personal risk management - rapid evidence generation - SARS-CoV-2

Since its global recognition in December 2019, the novel coronavirus disease (COVID-19) pandemic has spread to over 200 countries in less than five months. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of this disease, was noted to spread efficiently through respiratory droplets and contact routes¹⁻⁴. While common presenting symptoms are fever, fatigue, dry cough, myalgia and dyspnoea, a few patients have reported having diarrhoea, nausea, vomiting and new-onset anosmia or ageusia. A considerable proportion of the SARS-CoV-2-infected individuals (around 80%) did not have any noticeable symptoms and yet were able to transmit the infection⁵. Such unique transmission potentials of SARS-CoV-2 and lack of definitive antiviral therapy were the reasons behind its wide-scale spread. Evidence indicates that healthcare workers (HCWs) are particularly at risk of acquiring SARS-CoV-2 infection, due to repeated occupational exposure⁶.

In the absence of specific treatments against COVID-19, social distancing⁷, use of face masks⁸ and frequent hand washing with alcohol rubs or soap constituted the infection prevention measures targeting general population⁹. However, HCWs, being exposed to a higher quantum of risk, needed additional intervention approaches for protection¹⁰. Aprons, gowns, gloves, masks, face shields and goggles addressed such needs. These protective gears serve useful purpose in settings where procedures such as nasopharyngeal swab collection, endotracheal intubation or respiratory suctioning are performed on suspected or confirmed patients of COVID-19, potentially generating aerosols from the respiratory tract¹¹. However, caregiving in a pandemic situation would also entail the risks of transmission of SARS-CoV-2 infection to HCWs from asymptomatic individuals who are not necessarily undergoing invasive procedures^{2,12,13}. Chemoprophylaxis for HCWs could potentially have add-on advantages to cover this additional risk.

Prophylaxis in the present context refers to the use of a short-term therapy to prevent acquisition

of SARS-CoV-2 infection. Currently, there are no approved vaccines against SARS-CoV-2, which makes the alternative of using chemotherapeutic agents an attractive proposition. However, no antiviral medicines proved efficacious during the previous coronavirus outbreaks (SARS 2003; Middle East respiratory syndrome coronavirus 2012) and therefore, did not leave the therapeutic community with any viable options during the present COVID-19 pandemic^{14,15}. Hydroxychloroquine (HCQ) came into discussion against this background¹⁶. Ability of this compound to inhibit the infection by SARS-CoV-2, as well as viral replication in cell cultures in a time- and dose-dependent manner made it a primary choice¹⁷. Furthermore, HCQ elevates the pH of endosomes and inhibits SARS-CoV-2 RNA-mediated inflammatory response¹⁸. These laboratory findings encouraged researchers to consider HCQ, originally used for malaria, as a repurposed agent for prophylaxis against SARS-CoV-2¹⁹.

The National Task Force for COVID-19 in India took cognizance of this evidence and empirically recommended the use of HCQ as prophylaxis against SARS-CoV-2 infection in asymptomatic HCWs treating suspected or confirmed COVID-19 cases. Asymptomatic household contacts of confirmed COVID-19 cases were also covered by this advisory released on March 22, 2020²⁰. Around the same time, in South Korea, HCQ prophylaxis was used successfully to avert new infections after a large COVID-19 exposure event in a long-term care facility²¹. Scientific communications further underlined the necessity of examining the utility of such approaches in the context of high-burden, high-income countries such as Italy²². Against this backdrop, a case-control investigation was conducted to compare the risks of and protective factors against SARS-CoV-2 infection among HCWs in India.

Material & Methods

The ICMR COVID-19 Research Team developed the study proposal, which was approved by the ICMR

Central Ethics Committee. Data collection for this investigation was done during May 8-23, 2020. Each participant was informed about the study purpose, and verbal consent was obtained before proceeding with telephonic interview. A data portal developed to capture the information regarding individuals undergoing testing for SARS-CoV-2 infection across India was used to identify the study participants. HCWs tested between the first week of April 2020 and the end of first week of May 2020 formed the sample pool, from which cases and controls were drawn. Symptomatic HCWs testing positive on real-time reverse transcription-polymerase chain reaction (qRT-PCR) for SARS-CoV-2 were defined as cases. Controls were symptomatic HCWs who tested negative on qRT-PCR for SARS-CoV-2 under similar considerations.

Measures: A brief 20-item interview schedule was developed to elicit the information on key issues, such as department, designation and length of employment, and use of personal protective equipment (PPE). Among exposure variables, the HCW was asked about contact with suspected or confirmed COVID-19 patients on ventilator and involvement in aerosol-generating procedures (AGPs) such as nasopharyngeal swab collection, endotracheal intubation and respiratory suction. To minimize recall bias, this enquiry was restricted to seven days before SARS-CoV-2 testing. A history of prophylactic HCQ intake with dosing details was also obtained.

Telephonic interviews: Participants were telephonically contacted by the researchers to introduce themselves, verify identities, describe the study purpose and check availability for interviews. If a participant's contact phone number in the ICMR data portal actually belonged to a treatment supporter or caregiver or relative, we reached out to the individual who was tested for COVID-19 through the primary contact. Following verbal consent, telephonic interviews, which took 5-11 min, were conducted. At the close of the interviews, participants' queries related to COVID-19 were addressed.

Sample size: It was intended to enrol cases and controls in a 1:1 ratio and match them for location (testing centre) and temporality (test date). Assuming that 50 per cent of the controls were on HCQ prophylaxis (exposure) and correlation coefficient for exposure between matched cases and controls would be 0.2, it was estimated that 484 cases would be required to detect an odds ratio of 1.50 with 80 per cent power at five

per cent significance level²³. These calculations were undertaken using Power Analysis Sample Size (PASS) software version 11.0²⁴.

Statistical analysis: The data captured in hard copies during the telephonic interviews were checked for quality and computerized following the necessary corrections. The association of key risk factors with SARS-CoV-2 infection was examined by comparing distributions of cases and controls across different exposures. Variables which had biologically plausible association with the outcome and were relevant for planning strategies for the prevention of SARS-CoV-2 infection in HCWs were entered into a standard logistic regression model²⁵. STATA version 13.1 (StataCorp LP, College Station, TX, USA) was used for data analysis including trend analysis by Chi-square test.

Results

The ICMR data portal contained the results and contact details of 23,898 symptomatic HCWs who were tested for SARS-CoV-2 infection. After excluding non-Indian nationals and missing or wrong contact details from this database, 21,402 records were obtained, with 1,073 (5%) confirmed SARS-CoV-2-infected HCWs. Although it was initially decided to contact 650 cases and controls each (accounting for 25% loss over the calculated sample size of 484), only 624 and 549 individuals could be contacted in the case and control groups, respectively. Completed interview schedules of 60.58 per cent of cases (378/624) and 67.94 per cent of controls (373/549) were available for analysis. The reasons for not being able to reach out to some of the participants were: calls not picked up, wrong numbers, ineligible candidates (not HCWs), consent refusal to name a few.

Fifty eight per cent of the cases and about half of the controls were males. While the mean age of the cases was 34.73 yr [\pm standard deviation (SD): 9.64; median: 33.0; interquartile range (IQR): 27-40], the mean age of the controls was 33.47 yr (\pm SD: 9.77; median: 31.0; IQR: 26-38). Age distribution did not follow Gaussian distribution in either group. Table I presents details of the study participants.

Vulnerability of HCWs: Vulnerability of the study participants to SARS-CoV-2 infection was ascertained through a history of (i) placement in intensive care unit (ICU) catering to suspected or confirmed COVID-19 cases, (ii) procedures such as nasopharyngeal swab collection, intubation, respiratory suctioning and

Table I. Profile of the healthcare workers included in the study

Parameters	Cases (n ₁ =378) (%)	Controls (n ₂ =373) (%)	OR	95% CI of OR	P
Gender					
Male	219 (57.95)	188 (50.40)	1.36	1.02-1.81	0.038
Female	159 (42.06)	185 (49.60)	Ref		
Age (yr)					
18-25	65 (17.2)	86 (23.06)	0.62	0.35-1.09	0.208
26-33	134 (35.45)	135 (36.19)	0.81	0.48-1.38	
34-41	97 (25.66)	77 (20.64)	1.04	0.59-1.8	
42-49	43 (11.38)	43 (11.53)	0.82	0.44-1.54	
>50	39 (10.32)	32 (8.58)	Ref		
Occupation					
Doctor	111 (29.37)	123 (32.98)	0.94	0.57-1.57	0.537
Nurse/ANM	165 (43.65)	144 (38.61)	1.2	0.74-1.96	
Housekeeping staff	16 (4.23)	10 (2.68)	1.68	0.68-4.14	
Security guards	10 (2.65)	12 (3.22)	0.88	0.34-2.25	
Others	36 (9.52)	42 (11.26)	0.9	0.48-1.67	
Laboratory technician/operation theater technician	40 (10.58)	42 (11.26)	Ref		
Duration of work in respective workplace before COVID-19 testing (yr)					
>1	264 (69.84)	179 (47.99)	2.51	1.86-3.39	<0.001
<1	114 (30.16)	194 (52.01)	Ref		

OR, odds ratio; CI, confidence interval; Ref, reference category; ANM, auxiliary nurse midwife

clinical specimen handling by HCWs and (iii) use of PPE. Endotracheal intubation was associated with higher odds of SARS-CoV-2 infection. Respondents who reported never using PPEs were also at a higher risk. On the other hand, when the participants were asked about individual components of PPE, usage of masks, caps, gowns and gloves was associated with reduced odds of acquiring SARS-CoV-2 infection (Table II).

Hydroxychloroquine prophylaxis: Distribution of cases and controls across exposures in univariate analysis indicated the association of risk ($P=0.087$) of SARS-CoV-2 infection with the lack of HCQ prophylaxis (Table III). However, the number of maintenance doses taken by HCWs following the intake of a loading dose revealed a protective dose-response relationship. Consumption of four or more maintenance doses was associated with a significant decline in the risk of SARS-CoV-2 infection among the study participants (Figure). The significant declining trend had an overall χ^2 value of 48.88 ($P<0.001$).

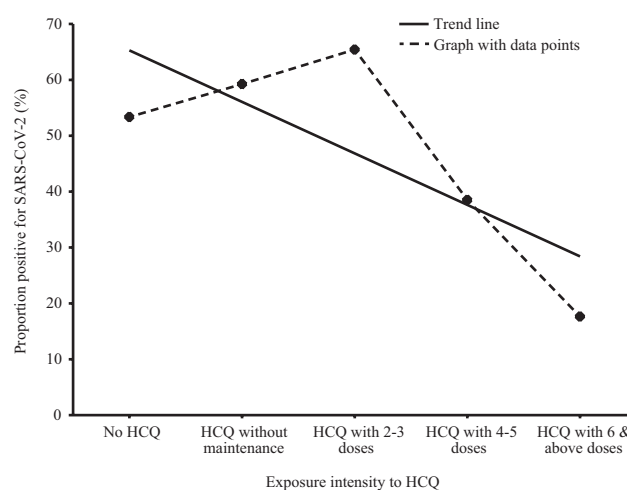


Figure. Dose-response relationship between hydroxychloroquine (HCQ) exposure and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Of the 172 cases and 193 controls reporting HCQ intake, no significant difference in the occurrence of adverse drug reactions was noted. The three most common side effects of HCQ as reported by the cases and controls were nausea (5 vs. 8%), headache (6 vs. 5%)

Table II. Place of work, procedure and protection details of healthcare workers

	Cases (n ₁ =378) (%)	Controls (n ₂ =373) (%)	OR	95% CI of OR	P
ICU with suspected or confirmed COVID-19 cases on ventilator					
Yes	53 (14.02)	40 (10.72)	1.36	0.88-2.1	0.17
No	325 (85.98)	333 (89.28)	Ref		
Nasopharyngeal swab collection					
Yes	18 (4.76)	22 (5.9)	0.8	0.42-1.51	0.488
No	360 (95.24)	351 (94.1)	Ref		
Endotracheal intubation					
Yes	22 (5.82)	9 (2.41)	2.5	1.13-5.5	0.01
No	356 (94.18)	364 (97.59)	Ref		
Respiratory tract suctioning					
Yes	15 (3.97)	20 (5.36)	0.73	0.37-1.45	0.365
No	363 (96.03)	353 (94.64)	Ref		
Handling clinical specimen (stool, blood, bronchoalveolar lavage)					
Yes	42 (11.11)	46 (12.33)	0.89	0.57-1.39	0.603
No	336 (88.89)	327 (87.67)	Ref		
PPE usage					
Never used	57 (15.08)	17 (4.56)	3.72	2.12-6.52	<0.001
Used in all or some cases	321 (84.92)	356 (95.44)	Ref		
Use of PPE gears					
Masks					
Any mask use	310 (82.01)	346 (92.76)	0.35	0.22-0.57	<0.001
No mask use	68 (17.99)	27 (7.24)	Ref		
Cap					
Yes	166 (43.92)	196 (47.45)	0.7	0.53-0.94	0.018
No	212 (56.08)	177 (52.55)	Ref		
Gown					
Yes	152 (40.21)	194 (52.01)	0.62	0.46-0.83	0.001
No	226 (59.79)	179 (47.99)	Ref		
Shoe cover use					
Yes	133 (35.19)	127 (34.05)	1.05	0.78-1.42	0.743
No	245 (64.81)	246 (65.95)	Ref		
Face shield or goggles					
Yes (either or both)	163 (43.12)	180 (48.26)	0.81	0.61-1.08	0.158
No (none)	215 (56.88)	193 (51.74)	Ref		
Gloves					
Yes	267 (70.63)	322 (86.33)	0.38	0.26-0.55	<0.001
No	111 (29.37)	51 (13.67)	Ref		

PPE, personal protective equipment; ICU, intensive care unit

Table III. Patterns of hydroxychloroquine (HCQ) prophylaxis in healthcare workers

Parameters	Cases (n ₁ =378) (%)	Controls (n ₂ =373) (%)	OR	95% CI of OR	P
HCQ prophylaxis					
No	206 (54.5)	180 (48.26)	1.28	0.96-1.71	0.087
Yes	172 (45.50)	193 (51.74)	Ref		
Number of maintenance doses of HCQ prophylaxis taken					
>6	12 (3.17)	56 (15.01)	0.19	0.1-0.36	<0.001
4-5	42 (11.11)	67 (17.96)	0.55	0.35-0.84	
2-3	70 (18.52)	37 (9.92)	1.65	1.06-2.58	
HCQ loading dose and irregular recall of maintenance	48 (12.7)	33 (8.85)	1.27	0.78-2.07	
None	206 (54.5)	180 (48.26)	Ref		
Combination prophylaxis					
HCQ only	130 (34.39)	133 (35.66)	0.85	0.62-1.17	0.002
HCQ+azithromycin+vitamins	25 (6.61)	16 (4.29)	1.36	0.71-2.64	
HCQ+vitamins	6 (1.59)	25 (6.70)	0.21	0.08-0.52	
HCQ+non-allopathic systems of medicines or others	11 (2.91)	19 (5.09)	0.51	0.23-1.09	
No HCQ	206 (54.5)	180 (48.26)	Ref		

and diarrhoea (5 vs. 4%). While none of the controls on HCQ complained of palpitations, only one case (1/172, 0.6%) reported the same. Gastrointestinal symptoms such as acidity and vomiting following HCQ intake ranged from 0.6 per cent in cases to about two per cent in controls. Very few cases (0.6%) and controls (1.4%) had skin rashes after consuming HCQ.

Multivariate analysis: Factors found associated ($P<0.1$) with SARS-CoV-2 infection among HCWs in univariate analysis and having biological plausibility were entered into multivariate model. In case of conceivable similarity between explanatory variables, one was chosen over another to avoid collinearity. For example, PPE rather than individual items (cap, mask, gown, glove, *etc.*) of PPE was included in the model. Adjusted for²⁵ gender, use of PPE, endotracheal intubation, different intensity of exposure to prophylactic HCQ and testing place with date, intake of 4-5 maintenance doses of HCQ [adjusted odds ratio (AOR): 0.44; 95% confidence interval (CI): 0.22-0.88; $P=0.02$] was found to independently impart the protective effect against SARS-CoV-2 infection among HCWs (Table IV). Notwithstanding this effect, the advantage of PPE usage was also independently indicated by the multivariate model. Noticeably, six or more prophylactic doses of HCQ used by HCWs had a remarkably high (>80%) protective effect against SARS-CoV-2 infection.

Discussion

Research to inform public health responses during infectious disease emergencies is gradually gaining importance worldwide. For example, Ebola virus disease in West Africa and Nipah virus outbreak in the Indian sub-continent required quick research responses to help mitigate human sufferings in the recent past^{26,27}. The current investigation can be considered as an example of this emerging trend. We leveraged a nationwide COVID-19 testing database to rapidly generate evidence to inform public health action.

The pivotal finding of our study was the noteworthy benefits of HCQ prophylaxis. It was identified that simply initiating HCQ prophylaxis did not reduce the odds of acquiring SARS-CoV-2 infection among HCWs. However, with the intake of four or more maintenance doses of HCQ, the protective effect started emerging, and in the adjusted multivariate model, a significant reduction (>80%) in the odds of SARS-CoV-2 infection in the HCWs was identified with the intake of six or more doses of HCQ prophylaxis. This dose-response relationship (Figure) added strength to the study outcomes. Worth noting in this context was that the National Task Force for COVID-19 in India recommended once a week maintenance dose for seven weeks (400 mg once weekly), following the loading dose (400 mg bd).

Table IV. Factors independently associated with SARS-CoV-2 in healthcare workers in India

Attributes	AOR	95% CI of AOR	P
Male	1.93	1.21-3.07	0.006
Never used PPE	5.33	2.27-12.48	<0.001
Performing endotracheal intubation	4.33	1.16-16.07	0.029
Maintenance doses of HCQ			
HCQ loading dose and irregular recall of maintenance	1.87	0.82-4.24	0.136
2-3	2.34	1.23-4.83	0.022
4-5	0.44	0.22-0.88	0.02
≥6	0.04	0.01-0.16	<0.001
AOR, adjusted odds ratio; HCQ, hydroxychloroquine			

Adherence to this recommended regimen is underlined by the findings of the present study. The potential antiviral and anti-inflammatory properties of HCQ²⁸, together with the low cost of therapy, excellent oral bioavailability²⁹, high tissue concentrations in the lungs relative to the plasma levels and acceptable safety profile lend support to this assertion¹⁷. However, HCQ prophylaxis should be taken in tandem with PPE use as indicated by the multivariate model (Table IV).

A recent registry-based analysis highlighted that HCQ did not offer therapeutic benefits to severe COVID-19 cases, and was associated with increased mortality³⁰. This apparent disparity with the findings of the current investigation could be explained by the two different application contexts. While the observational study involving registry-analysis focussed on the treatment of hospitalized COVID-19 patients, our emphasis was on the prevention of infections among HCWs. In treatment settings, severe COVID-19 patients are likely to have a very high viral load and cytokine levels, which may not be improved by HCQ therapy³¹. The registry-based analysis further recorded higher frequencies of ventricular arrhythmias in patients receiving HCQ. The toxicities of HCQ are likely to be infrequent in healthy groups undergoing prophylactic therapy as observed in our study participants. Biologically, it appears plausible that HCQ prophylaxis, before onset of infection, may inhibit the virus from gaining a foothold.

While the strength of the present analysis was the involvement of a countrywide database that drew upon more than 70 COVID-19 testing laboratories spread all over India, its limitations were rooted in its observational design. However, in the absence of clinical trial results³² on safety and efficacy of HCQ chemoprophylaxis in the HCWs, this study

offers evidence of public health importance. Higher prevalence of SARS-CoV-2 infection in the HCWs has been a global concern, including in countries such as Spain, Italy and the USA³³⁻³⁵, which further underscores the importance of the present findings.

The first part of the dose-response relationship curve showed an apparent increase in the odds of acquiring SARS-CoV-2 infection in HCWs who had taken 2-3 doses of HCQ prophylaxis. While this phenomenon cannot be fully explained by the data collected through the present study, lessons from other areas of public health could be of some help. The parallels³⁶ include (i) seat-belt legislations *vis-à-vis* speeding and road traffic casualties, and (ii) condom use promotion with unintended effects linked to greater sexual activities. Adams³⁷ and Wilde³⁸ allude to models of individual risk management which have the potential to explain such apparent paradoxes. They described that the introduction of a safety device could disrupt the balance between perceived hazards and rewards of risk-taking behaviours. Within the ambit of the present discussion, we consider (i) HCQ prophylaxis as a newly identified safety device, (ii) getting infected with SARS-CoV-2 as the perceived hazard, and (iii) not adhering to conventional respiratory infection prevention measures, such as PPE use, personal hygiene and social distancing as risk-taking behaviours.

In conclusion, public health message on the role of HCQ prophylaxis for the prevention of SARS-CoV-2 infection among HCWs emerging from this study should be considered with the existing understanding of risk homeostasis operating at individual levels.

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For correspondence: Dr Samiran Panda, ICMR-National AIDS Research Institute, 73-G, MIDC, Bhosari, Post Box No. 1895, Pune 411 026, Maharashtra, India
e-mail: director@nariindia.org