ORIGINAL ARTICLE

Hydroxychloroquine for SARS CoV2 Prophylaxis in Healthcare Workers – A Multicentric Cohort Study Assessing Effectiveness and Safety

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Abstract

Background, Objective: We studied the effectiveness and safety of Hydroxychloroquine (HCQ) preexposure prophylaxis against COVID-19 in Healthcare workers (HCWs) previous studies being inconclusive due to small sample and lack of risk stratification

Design and setting: Prospective, observational, multicenter cohort study in 44 hospitals in 17 Indian states during May-Sept 2020

Participants: 12089 Consenting Doctors, nurses, ancillary staff likely exposed to COVID-19 patients irrespective of whether taking HCQ preexposure prophylaxis (4257) or not(7826) participated,(in 6 data missing)

Measurements: Data was collected on a self administered online questionnaire. Statistical analysis was done on SPSS version 20.

Results: Age above 45 years, diabetes, hypertension, history of COVID contact were independent risk factors for COVID positivity. HCQ intake did not show an independent association. However, when adjusted for other risk factors, HCQ dose as per Government recommendations, 2-3, 4-5 and 6 or more weeks reduced the probability of COVID positivity by 34%, 48%, 72% respectively. COVID free median survival time was higher in non-diabetics, non-hypertensives, persons below 45 years, with no prior exposure to COVID case and those who took HCQ for more than 6 weeks With modeling extent of risk reduction under different scenarios of risk and HCQ intake was 1-65% . Major adverse events reported were GI disorder, palpitation, giddiness and 140 persons discontinued due to adverse events.

Limitations: Limitation of self reporting by HCWs in online form, minimized by specified options,mandatory fields and telephonic verification

Conclusion: The study examined individual risk factors including site variations and found that HCQ 800 mg loading followed by 400 mg weekly, dose for more than 2 weeks, reduced the risk of COVID-19, in HCWs, and is a useful option in low resource settings till vaccines are made accessible to all.

Trial registration: CTRI/2020/05/025183

Introduction

Morbidity and mortality are reported worldwide amongst health care workers (HCWs) with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1,2] Hydroxychloroquine (HCQ), with an established safety profile, inhibits viral replication and inflammatory response, prompting its use for SARS-Co-V-2.[3,4]

There is no conclusive evidence for pre-exposure prophylactic use of HCQ in HCWs. A systematic review advises caution while interpreting studies.[5] Most studies have limitations of insufficient sample size and the absence of risk stratification.[5-7]

Vaccines have limitations of efficacy against emerging SARS- CoV-2 variants, long- term efficacy and safety. Continued research on existing and affordable medicines such as HCQ is therefore needed. We report here a large multicenter prospective cohort study on HCWs, comparing HCQ and no HCQ for pre-exposure prophylaxis and the impact of age, gender, comorbidities, and exposure to SARS-CoV-2 cases, on HCQ effectiveness and safety.

Methods

This prospective, observational, multicenter cohort study in 44 hospitals in 17 states of India included HCW's (doctors, nurses, allied staff) who were either taking or not taking prophylactic treatment for COVID-19 and were likely to be exposed to COVID 19 cases. There were no exclusion criteria.

Consenting HCWs, filled an online questionnaire, sent by e-mail or free messaging application, with information and consent. They provided information from the time they started prophylactic treatment until the date of filling the questionnaire. If

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Table 1: Baseline characteristics and chemoprophylaxis status

Characteristic	Categories	Numbers (%, n =12089)
Age	≤ 45 years	10461 (86.53%)
	> 45 years	1628 (13.47%)
Gender	Male	5731 (47.43%)
	Female	6351 (52.57%)
	Other	7
Comorbidities encountered*	Hypertension	544 (4.50%)
	Other cardiovascular disease	120 (0.99%)
	Diabetes	371 (3.07%)
	Recurrent respiratory infection or chronic respiratory disease	169 (1.40%)
	Known hypersensitivity to prophylaxis drugs	64 (0.53%)
	Retinopathy	35 (0.29%)
	G6PD deficiency	6 (0.055%)
	Others	359 (2.97%)
Chemoprophylaxis received*	No HCQ (No drug 7733, other drugs 93)	7826 (64.7%)
	Hydroxychloroquine	4257 (35.2%)
	Data Missing	6
Reasons for not taking HCQ prophylaxis or discontinuing prophylaxis*	Not convinced of effect	1397 (11.56%)
	Apprehensive of adverse effects	581 (4.81%)
	Experienced adverse effects	140 (3.29%)
	Had contraindication for the drug	35 (0.29%)
	Finished 7 weeks and did not know whether to continue	1083 (8.96%)
	Drug not available	210 (1.74%)
	Hospital supply did not continue	179 (1.48%)
	Developed COVID-19 infection	312 (2.58%)
	No reason given	4389 (36.33%)

*May be overlapping for individual subjects. Participants who discontinued HCQ are reflected in respective HCQ use group depending on dose taken till discontinuation. Participants who took other drugs eg., chloroquine, azithromycin, homeopathy are clubbed as No HCQ, since numbers are small and effectiveness of other drugs is unknown.

required, HCWs were given a printed questionnaire in the local language, with information transcribed to the online form. The proportion of missing data was negligible since most fields were mandatory.

The questionnaire (53 items) captured information on sociodemography, presence of co-morbidities, whether prophylatic drugs were used, not used or discontinued, investigations before and after prophylactic drugs, adverse effects experienced, exposure to COVID-19 cases, preventive protective equipment (PPE) used, COVID-19 infection symptoms, test(RT PCR for SARS CoV2) results and hospitalization/quarantine data.

The data transferred to cloud storage service, (data privacy and confidentiality ensured) was available to authorized persons at the sites for data verification and rectification. Reporting bias was avoided by telephonic contact with the participants. Allocation of HCQ or no HCQ was as per the participants choice. Investigators did not influence the choice thereby avoiding selection bias. Data verification for any systematic measurement error was done to avoid information bias. Confounding effect was addressed in the logistic regression analysis.

A formal sample size estimation was not possible when the study was planned as there was no reliable data on incidence of SARS CoV2 positivity or effectiveness of HCQ. Data collection was carried out from 23rd May to 15th September 2020 and a total of 12,089 HCWs were enrolled.

Statistical analysis

The descriptive summary data as mean (SD) for continuous variables and proportions for categorical variables was calculated. Quantitative variables eg., weeks of HCQ use, age, were grouped as previously described. Univariate and binary logistic regression models were fitted to assess the unadjusted and adjusted associations of gender, self-reported diabetes, hypertension, chronic respiratory disease, suspected or confirmed contact with a COVID case and pre-exposure prophylaxis of HCQ with different dosages, duration of intake, likelihood of being tested positive for SARS CoV2 and sites. Separate analysis was done for Mumbai, Delhi, Bhopal and Indore sites based on proportion tested in relation to numbers taking HCQ in standard recommended dose (400 mg twice on Day 1 loading dose followed by 400 mg weekly). Participants from all other sites with limited testing and/or high non-standard HCQ use or no HCQ use were grouped as 'other sites.' Interaction terms were added in the logistic regression model but are not reported as it did not improve predictive accuracy of the model.

Survival analysis (COVID free survival time)

For survival analysis, the primary end point was RTPCR confirmed COVID-19 positivity. For those on drug prophylaxis, the day of initiation and the day when the person tested positive were considered for survival analysis. For those who took no HCQ prophylaxis, we assumed the survival time as the number of weeks elapsed from 1st April 2020 (after the Government regulations on HCQ use was brought out) to the time they were tested or when they filled the form, when the study stopped, whichever came first.

Kaplan Meir survival analysis (KM) was done to compare the COVID free survival times and estimate median survival time. Log rank test was employed to compare the median survival times between age group, gender, selected co-morbidities, contact with a suspected or confirmed case, sites, and pattern of HCQ intake. Cox proportional hazard model was employed to assess the effect of variables on 'survival' time in relation to the hazard of experiencing COVID positivity.

Results

Site and participant characteristics

Of the 115,021 HCWs in the 44 sites, there were 33,261 doctors (28.92%), 29,417 nurses (25.58%) and the rest were other categories. 23,091 HCWs likely exposed to COVID cases, were contacted irrespective of whether they took HCQ or not. Of these, 12,089 (52.32%) participated. The reasons for not participating could not be ascertained as this was an online form.

Table 1 summarizes baseline demographic, clinical and chemoprophylaxis status. (Flow chart of participants, and outcome is given in Appendix 1) The two groups (No HCQ and HCQ) were comparable for baseline characteristics (Appendix2).

Table 2: COVID-positivity stratified by baseline characteristics

		COVID positive N (%)	COVID negative N (%)	Total	P value	Unadjusted Odds ratio (95% CI)
All sites		1119 (41.0)	1608 (59.0)	2727		
HCQ use pattern	No HCQ	611 (41.5)	862 (58.5)	1473		Reference
	HCQ non-standard use					
	HCQ 400-400	19 (23.8)	61 (76.2)	80	0.002	0.44 (0.26-0.74)
	HCQ 400-200	10 (31.2)	22 (68.8)	32	0.245	0.64 (0.30-1.36)
	HCQ $800_{IRR-MAIN}$	57 (41.0)	82 (59.0)	139	0.914	0.98 (0.69-1.40)
	HCQ 2-3 w	80 (44.2)	101 (55.8)	181	0.489	1.12 (0.82-1.53)
	HCQ 4-5 w	88 (47.6)	97 (52.4)	185	0.114	1.28 (0.94-1.74)
	HCQ ≥ 6 w	247 (40.0)	370 (60.0)	617	0.540	0.94 (0.77-1.3)
Age group	≤ 45 years	928 (38.6)	1476 (61.4)	2404	< 0.001	Reference
	> 45 years	191 (59.1)	132 (40.9)	323		2.30 (1.82-2.92)
Gender	Male	592 (40.7)	861 (59.3)	1453	0.758	Reference
	Female	527 (41.4)	746 (58.6)	1273		1.02 (0.88-1.19)
Suspected or confirmed COVID contact	No	193 (34.5)	367 (65.5)	560	< 0.001	Reference
	Yes	203 (46.7)	232 (53.3)	435		1.66 (1.29-2.15)
	Maybe	723 (41.7)	1009 (58.3)	1732		1.36 (1.12-1.66)
Diabetes	No	1050 (39.9)	1581 (60.1)	2631	< 0.001	Reference
	Yes	69 (71.9)	27 (28.1)	96		3.85 (2.45-6.05)
Hypertension	No	1045 (40.3)	1547 (59.7)	2592	0.001	Reference
	Yes	74 (54.8)	61 (45.2)	135		1.80(1.27-2.54)
Other cardiovascular disease	No	1106 (41.0)	1593 (59.0)	2699	0.696	Reference
	Yes	13 (46.4)	15 (53.6)	28		1.25 (0.59-2.63
Chronic respiratory disease	No	1092 (40.8)	1585 (59.2)	2677	0.083	Reference
	Yes	27 (54.0)	23 (46.0)	50		1.70 (0.97-2.99)
Recurrent respiratory infections	No	1101 (41.6)	1544 (58.4)	2645	0.964	Reference
	Yes	16 (40.0)	24 (60.0)	40		0.70 (0.33-1.47)

Table 3: Adjusted odds ratios of predictors from binary logistic regression model

Variables	Adjusted OR (95%CI) for COVID-positivity	P value
Sites*		
Mumbai	12.79 (9.76-16.76)	<0.001
Delhi	2.45 (1.89-3.19)	<0.001
Bhopal and Indore	0.61 (0.46-0.81)	0.001
Age group		
More than 45 years	1.52 (1.14-2.02)	0.004
Hydroxychloroquine use pattern		
HCQ non-standard		
HCQ 400-400	0.60 (0.35-1.04)	0.07
HCQ 400-200	0.41 (0.17-0.99)	0.047
$HCQ800_{IRR-MAIN}$	0.77 (0.5-1.19)	0.24
HCQ standard		
HCQ 2-3 w	0.66 (0.45-0.96)	0.03
HCQ 4-5 w	0.52 (0.35-0.76)	0.001
HCQ ≥ 6 w	0.28 (0.21-0.37)	<0.001
Suspected or confirmed COVID contact		
Sure	1.43 (1.06-1.91)	0.018
Not sure	1.40 (1.12-1.75)	0.003
Co morbidities		
Diabetes	2.76 (1.60-4.74)	<0.001
Hypertension	0.88 (0.55-1.39)	0.58
Chronic respiratory disease	1.70 (0.89-3.24)	0.11

*(Appendix 3 details of sites)

Patterns of chemoprophylaxis use

800 mg (400mg twice a day on day 1) loading and 400 mg weekly was considered as the HCQ standard regimen as recommended by the Ministry of Health and Family Welfare, Govt of India.

Patterns of HCQ used were (n):

No HCQ: no drug or drugs other than HCQ (7826)

HCQ nonstandard regimens

HCQ 400-400: 400 mg loading, 400 mg weekly (1073)

HCQ 400-200: 400 mg loading, 200 mg weekly (114)

HCQ $800_{IRR-MAIN}$: 800 mg loading,400 mg for 1 week or irregular maintenance dose (439)

Other - dose schedules other than above with widely varying doses no further analysis done (75)

HCQ standard regimens

HCQ 2-3 w: 800 mg loading, 400 mg weekly for 2-3 weeks consecutively. (420)

HCQ 4-5 w: 800 mg loading, 400 mg weekly for 4-5 weeks consecutively (451)

HCQ ≥ 6 w: 800 mg loading, 400 mg weekly for six or more weeks consecutively (1685)

Univariate analysis (Table 2) does not reflect prophylactic benefit of HCQ use. Variables independently associated with COVID positivity, were age group > 45 years, contact with a confirmed or suspected COVID case, co-morbidities of diabetes, hypertension and chronic respiratory disease.

Data on use of PPE was captured. However, as all HCWs were using PPE as recommended, non-use of PPE was not analyzed as a risk factor.

Adjusted odds ratios (Table 3) taking the covariates with p value < 0.15, patterns of HCQ use and sites (Individual city data is given in Appendix 3, each city may have more than one site, COVID 19 positivity/01 million population, in states over period under study is given in Appendix 4) as explanatory variables in binary logistic regression model, indicate that HCQ use with recommended dose provides protection. HCQ for 2-3 weeks, 4-5 weeks or more than 6 weeks significantly reduced COVID positivity by 34%, 48% and 72% respectively. Compared to other sites, HCWs in Mumbai were 12.8 times, and Delhi 2.5 times more likely to be COVID positive, keeping other variables constant.

Modeling indicates that the level of protection with HCQ varies with dosing, duration of use and interplay of various risk factors. including site variation (Table 4).

Hospitalization due to COVID-19 and course in hospital

Of 886 hospitalizations for COVID-19, 791 (89.28%) were mild, 23 were moderate (2.6%) requiring ICU admission and 4 were severe requiring assisted ventilation (information was missing in 68). There was no significant difference in the course of hospitalization between HCQ and no HCQ use (Appendix 5).

Adverse events in HCQ group

Adverse events (AE) were mild (summarized in Appendix 6), with the younger and female gender having more AEs.

Sixteen serious AEs (severe nausea, vomiting, abdominal pain, palpitations, fainting, visual disturbance, hypersensitivity), needing at least one day hospitalization were reported. However, the study design precluded a definitive causality analysis for these events.

Baseline ECG in 601 (14.1%) and subsequent ECG in 202 (4.75%) showed abnormality in 47 (1.10%). Details were not specified and causality analysis was not done.

Table 4: Representative scenarios from logistic regression model indicating extent of risk reduction with different duration of HCQ use, in the presence of risk factors at different sites

Representative scenario from logistic regression model	HCQ use	Probability of COVID positivity	% reduction in probability of positivity in HCQ users
HCW at or below 45 years from Mumbai, who is non-diabetic, not having chronic respiratory disease with probable recent contact with a COVID case	No HCQ	82%	
	HCQ 2-3 weeks	75%	9%
	HCQ 4-5 weeks	70%	15%
	HCQ ≥ 6 weeks	56%	32%
HCW from Mumbai above 45 years who is diabetic, having chronic respiratory disease with sure recent contact with a COVID case	No HCQ	96%	
	HCQ 2-3 weeks	95%	1%
	HCQ 4-5 weeks	93%	3%
	HCQ ≥ 6 weeks	88%	8%
HCW from Delhi below 45 years who is non-diabetic, not having chronic respiratory disease with probable recent contact with a COVID case	No HCQ	55%	
	HCQ 2-3 weeks	44%	20%
	HCQ 4-5 weeks	38%	31%
	HCQ ≥ 6 weeks	25%	55%
HCW from Delhi above 45 years who is diabetic, having chronic respiratory disease with sure recent contact with a COVID case	No HCQ	83%	
	HCQ 2-3 weeks	76%	8%
	HCQ 4-5 weeks	71%	14%
	HCQ ≥ 6 weeks	57%	31%
HCW from Bhopal/Indore below 45 years who is non-diabetic, not having chronic respiratory disease with sure recent contact with a COVID case	No HCQ	23%	
	HCQ 2-3 weeks	17%	26%
	HCQ 4-5 weeks	14%	39%
	HCQ ≥ 6 weeks	8%	65%
HCW from Bhopal/Indore above 45 years who is diabetic, having chronic respiratory disease with probable recent contact with a COVID case	No HCQ	45%	
	HCQ 2-3 weeks	35%	22%
	HCQ 4-5 weeks	30%	33%
	HCQ ≥ 6 weeks	19%	58%

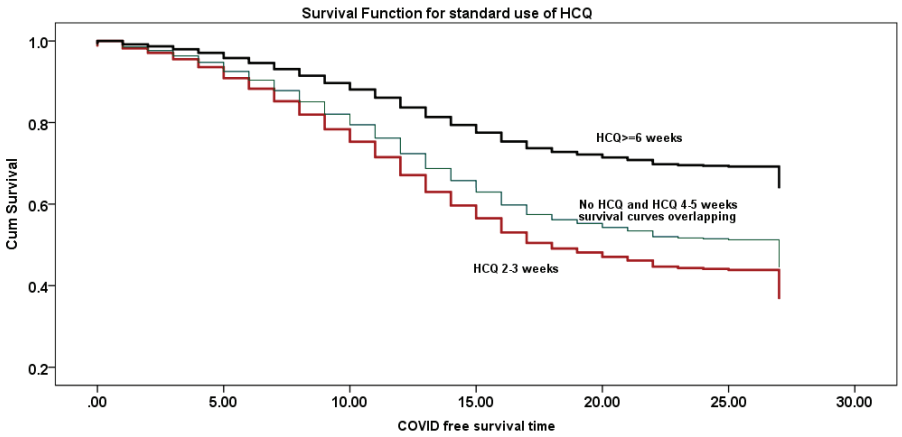

Fig. 1: Survival plots for COVID-positivity, stratified by pattern of HCQ use after adjustment for other covariates

COVID free survival analysis

A 'COVID free survival' analysis was done by log-rank and generalized Wilcoxon (Breslow's) test, for COVID positivity in HCQ and No HCQ participants (whose date of testing was available). It indicates a significant difference among the plots ($p < 0.001$) for patterns of HCQ use, taking no HCQ use being the reference category.

Using Kaplan Meir analysis, individuals below age 45 years, non-diabetics, non-hypertensives and participants without chronic respiratory disease, had longer COVID free survival time (Appendix 7).

Cox proportional hazard modeling (Appendix 8, 9; Figure 1) shows that for individuals who took HCQ for 6 weeks or more, the COVID hazard was 45% less compared to taking no HCQ. Participants from Mumbai had an increased hazard of COVID positivity by 5.4 times, and those from Delhi 2 times, as compared to other sites.

Discussion

Findings and strengths of the present study

Our study is the largest multicenter study on HCQ prophylaxis in HCWs, covering over 12000 HCWs at risk of COVID-19.Using univariate analysis, age, comorbidities, exposure to COVID cases, but not HCQ use, were independently associated with higher SARS CoV-2 positivity. Cook et al noted that many risk factors are linked.[8] Univariate analysis alone may be misleading in an epidemiological study.

With binary logistic regression analysis, HCQ use in recommended dosing for 2-3, 4-5 and 6 weeks or more, provided significant protection (adjusted odds ratios 0.66, 0.52 and 0.28 respectively, with upper bound of the corresponding 95% CI being < 1), when adjusted for risk factors. The extent of protection calculated by modelling varied based on different sites, risk factors and duration of HCQ use. HCQ use for 6 weeks or more provided protection to the extent of 8 to 65%. In Cox proportional hazard modeling with HCQ for 6 weeks or more, the COVID hazard was 45% less compared to no HCQ.

These results indicate real world scenarios with possibility of generalizability, extrapolation. and importance from a public health perspective. As vaccines have varying levels of efficacy and other challenges, these findings regarding HCQ are important to consider as complementary strategies for prophylaxis.

Comparison with other studies

Publications on pre-exposure prophylactic use of HCQ in HCWs have provided contradictory results. Results of RCTs have not shown benefit, though small sample size and non-stratification for risk factors were limiting factors. In a double-blind RCT in 132 hospital based HCWs with HCQ 600 mg daily or placebo for 8 weeks, the incidence of COVID-19 was 6.3% for HCQ group and 6.6% for placebo.[9] In another RCT with 1483 HCWs, in USA and Canada, participants were randomized to HCQ (400 mg once weekly or twice weekly for 12 weeks) or placebo. There were 0.27 events per person year with once weekly and 0.28 with twice weekly HCQ compared to 0.38 with placebo.

Chatterjee et al using multivariate analysis in a case control study noted significant decline in the odds of getting infected (adjusted OR 0.44; 95% CI 0.22 - 0.88) with HCQ for more than 4 weeks and a dose-response relationship

with duration of HCQ use.[7]

HCQ benefits can be overshadowed by other risk factors and therefore the benefits stand out only on multivariate analysis. The RCTs published till date have relied upon randomization for distribution of baseline confounders but have not attempted multivariate analysis. In a small cohort study, prophylactic HCQ usage was associated with lesser likelihood of developing SARS-CoV-2 infection (relative risk 0.193; 95% CI 0.071 - 0.526; p = 0.001). Confounding was limited by stratification. None of the HCQ users reported serious AE in this study.[10]

Optimum dose, frequency and duration of HCQ for prophylactic use

Regimens with a loading dose to reach target concentrations rapidly and maintenance dose to maintain the target concentration have been proposed through various studies. White et al[11] suggested that with *in-vitro* EC50 of 0.72 uM with 4:1 blood plasma ratio, putative in-vivo EC50 value (blood concentration) of HCQ should be 2.88 μM. However, this has to be balanced against the potential for adverse effects. In a simulation study from India, simulated blood concentration (with preexposure prophylaxis dose of 400 mg BD loading and 400 mg weekly maintenance), peak was 1.58 ± 0.34 μM, and trough 0.12 ± 0.03 μM on day 1, with similar concentrations at week 8.[12]

In the present study, with varying dosing regimens and irregularity in dosage, regimens that began with an 800 mg loading dose showed some degree of prophylactic benefit after adjusting for risk factors. Protection also appeared to increase with duration of use. Several studies are ongoing and their results may shed more light on optimum dosing.[13]

Adverse effects

Adverse events were more in the younger and female population in our study. Sixteen of these events (0.58%) were serious requiring more than one day hospital admission. 140 of the 4255 who started HCQ prophylaxis (3.29%) cited adverse effects as one of the reasons for discontinuing the same.

HCQ has a long history of safe use, except in individuals who are critically ill.[14] Two studies that reported increased adverse effects of HCQ when used in treatment of COVID-19 patients were retracted within days of publication.[15,16]

Psychiatric disorders have been reported.[17] However, no serious psychiatric effects have been reported from any studies in India so far.

Limitations

The study sites from different parts of the country had varying levels of incidence and transmission of SARS CoV2 giving an opportunity to assess the effect of variation between sites. The benefits of HCQ have been evident in the binary regression model with the variables independently associated with COVID positivity on univariate analysis, along with patterns of HCQ use and sites as explanatory variables.

As this is an observational study, and not randomized, it is possible that those less likely to be exposed may not have taken HCQ. However, the non HCQ group then will have inherently lower positivity.

The participating HCWs were from the study site hospitals and hence accessible for data verification. The limitation was that the online form used for data collection is dependent on reporting by HCW though verified by telephonic personal contact. However, as the online form had mandatory fields, missing data was minimal.

Conclusion and Policy Implications

Our study with over 12,000 HCWs, comparing HCQ with no HCQ for pre-exposure prophylaxis, taking cognizance of risk factors and site variation, shows that HCQ is effective in reducing risk of COVID-19, at 800 mg loading and 400 mg weekly dose with more than 2 weeks dosing. Protection improves as duration of intake increases to 6 weeks or more. Logistic regression modeling has indicated the extent of protection in different scenarios of risk factors. Overall, HCQ was well tolerated. Despite the limitation of an observational study relying on online data capture, the strengths of large sample size, wide geographical coverage and real-life effectiveness, assessment through multivariate analysis lends credence to the study findings. It may also explain the inconclusive results and lack of HCQ benefit observed in some studies. Vaccine has its own limitations, and therefore an alternative strategy of prophylaxis such as HCQ is important, especially in low resource settings.

Transparency declarations

All authors declare that they do not have any financial conflicts of interest and the funder(s) has/have not played any decision-making role in the research . All the authors state that there is no conflict of interest to declare.

We declare that we have not received the assistance of a professional medical writer or any other similar service from any agency. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare support from no other agency for the submitted work. The authors report no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval

All the sites obtained approval from their Institutional Ethics Committees to conduct the study. In addition, approval from the ICMR Central Ethics Committee on Human Research (CECHR) was obtained (NCDIR/BEU/ICMR-CECHR/75/2020 /13th May 2020)]. The study was registered on CTRI site - CTRI/2020/05/025183.

Data sharing

No additional data is available. All the authors affirm that the 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 have been explained.

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Author contributions

Badyal Dinesh, Kamat Sandhya, Hazra Avijit, Chandy Sujith, Kshirsagar Nilima wrote, edited, finalized the manuscript. Xavier Denis, Faruqui Atiya wrote the protocol and managed the online form, data verification. Menon Geetha and Rao Vishnu conducted statistical analysis. Medhi Bikash, RanjalkarJaya, Chugh Preeta Kaur, Tripathi Raakhi, Shetty Yashashri helped in drafting the manuscript, editing and uploading it.

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Authors had access to full datasets and contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors are guarantors and accept full responsibility for the work.

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