BMJ Open

Hydroxychloroquine plus personal protective equipment versus personal protective equipment alone for the prevention of laboratory-confirmed COVID-19 infections among healthcare workers: a multicentre, parallel-group randomised controlled trial from India

Bharath Kumar Tirupakuzhi Vijayaraghavan ,[1,2] Vivekanand Jha,[2] Dorrilyn Rajbhandari,[3] Sheila Nainan Myatra,[4,5] Arpita Ghosh ,[2] Amritendu Bhattacharya,[2] Sumaiya Arfin,[2] Abhinav Bassi,[2] Lachlan Hugh Donaldson,[3] Naomi E Hammond ,[6] Oommen John,[2] Rohina Joshi,[7] Mallikarjuna Kunigari,[2] Cynthia Amrutha,[8] Syed Haider Mehdi Husaini,[9] Subir Ghosh,[10] Santosh Kumar Nag,[11] Hari Krishnan Selvaraj,[12] Viny Kantroo,[13] Kamal D Shah,[14] Balasubramanian Venkatesh,[3,15,16] for the HOPE Investigators

To cite: Tirupakuzhi Vijayaraghavan BK, Jha V, Rajbhandari D, *et al*. Hydroxychloroquine plus personal protective equipment versus personal protective equipment alone for the prevention of laboratory-confirmed COVID-19 infections among healthcare workers: a multicentre, parallel-group randomised controlled trial from India. *BMJ Open* 2022;**12**:e059540. doi:10.1136/bmjopen-2021-059540

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059540).

Received 24 November 2021
Accepted 13 May 2022

For numbered affiliations see end of article.

Correspondence to
Dr Bharath Kumar Tirupakuzhi Vijayaraghavan; bharathkumartv@gmail.com

ABSTRACT

Objectives To determine whether hydroxychloroquine when used with personal protective equipment reduces the proportion of laboratory-confirmed COVID-19 among healthcare workers in comparison to the use of personal protective equipment alone.

Design Multicentre, parallel-group, open-label randomised trial. Enrolment started on 29 June 2020 and stopped on 4 February 2021. Participants randomised in HydrOxychloroquine Prophylaxis Evaluation were followed for 6 months.

Setting 9 hospitals across India.

Participants Healthcare workers in an environment with exposure to COVID-19 were randomised in a 1:1 ratio to hydroxychloroquine plus use of personal protective equipment or personal protective equipment alone. 886 participants were screened and 416 randomised (213 hydroxychloroquine arm and 203 personal protective equipment).

Intervention Participants in intervention arm received 800 mg of hydroxychloroquine on day of randomisation and then 400 mg once a week for 12 weeks in addition to the use of personal protective equipment. In the control arm, participants continued to use personal protective equipment alone.

Main outcome Proportion of laboratory-confirmed COVID-19 in the 6 months after randomisation.

Results Participants were young (mean age 32.1 years, SD 9.1 years) with low-comorbid burden. 47.4% were female. In the 6 months after randomisation (primary analysis population=413), 11 participants assigned to the hydroxychloroquine group and 12 participants assigned to the standard practice group met the primary endpoint (5.2% vs 5.9%; OR 0.85, 95% CI 0.35 to 2.07, p=0.72). There was no heterogeneity of treatment effect in any prespecified subgroup. There were no significant differences in the secondary outcomes. The adverse event rates were 9.9% and 6.9% in the hydroxychloroquine and standard practice arms, respectively. There were no serious adverse events in either group.

Conclusions and relevance Hydroxychloroquine along with personal protective equipment was not superior to personal protective equipment alone on the proportion of laboratory-confirmed COVID-19. Definitive conclusions are precluded as the trial stopped early for futility, and hence was underpowered.

Trial registration number CTRI/2020/05/025067.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our trial is the largest multicentre trial evaluating hydroxychloroquine prophylaxis for COVID-19 from a low and middle-income country setting.
⇒ The trial tested the dose of hydroxychloroquine recommended by the Indian regulatory agencies and had the longest follow-up duration among hydroxychloroquine trials.
⇒ Our trial included a diverse set of participants, both in terms of balance of men and women, but also in terms of the various healthcare worker roles.
⇒ The trial stopped early for futility, hence limiting any conclusions.
⇒ Our trial did not include a placebo arm or employ blinding.

INTRODUCTION

[1]There have been over 524,000,000 cases of COVID-19 with over 6.2 million deaths until 25th May 2022. In India, there have been over 500,000 deaths.[1 2] At the onset of the pandemic, neither vaccines nor drugs providing post-exposure prophylaxis were available. Given their role, healthcare workers (HCWs), particularly those on the front lines, were identified as the group at the highest risk of acquiring the infection. In the severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks, HCWs accounted for 21.1% and 19.1% of cases, respectively.[3 4] In data from China and Italy in the early stages of the COVID-19 pandemic, 3.8% and 9% of confirmed cases were among HCWs.[5 6] In subsequent reports, this proportion has ranged from 7% to 15%.[7]

Early reports indicated that hydroxychloroquine (HCQ) may provide effective prophylaxis against SARS-CoV-2 infection based on its ability to reduce binding of the virus to the ACE2 receptor, prevent cellular entry of the virus and inhibit viral replication.[8 9] This, in combination with the observation that HCQ possessed favourable pharmacokinetic characteristics and its proven track record of safety for non-COVID indications, provided sufficient justification for conducting trials evaluating HCQ for pre-exposure prophylaxis.[10–12] However, the published trials are underpowered, or have suffered from methodological limitations or were evaluating HCQ in a different population. Importantly, none of these trials were from a lower middle-income context, where the challenges are inherently different. HCWs, particularly in India, were at a higher risk because of the limited availability of personal protective equipment (PPE), the slow roll-out of vaccination programmes and the enormous case burden.

Early in the pandemic, the Indian Council of Medical Research (ICMR) recommended HCQ as prophylaxis for HCWs and simultaneously made a plea that 'proof of concept and pharmacokinetics studies be taken up expeditiously'.[13] In parallel, there were also reports of adverse events[14] including death following the use of HCQ as prophylaxis/treatment. There was thus an ethical and a public health imperative to rapidly evaluate its effectiveness and safety.

The HydrOxychloroquine Prophylaxis Evaluation (HOPE) trial was designed to evaluate the combination of HCQ along with PPE over the use of PPE in preventing COVID-19 infection among HCWs at risk.

METHODS

Study design and oversight

HOPE was an investigator-initiated, stratified, parallel-group, open-label, multicentre randomised controlled trial. From 29 June 2020 to 4 February 2021, we enrolled HCWs from nine hospitals across India. These centres were selected on the basis of them being designated COVID-19 centres by the Government of India or by virtue of being involved in the care of patients with confirmed COVID-19. Written informed consent was obtained from all participants.

The trial was designed and overseen by a steering committee. An independent data and safety monitoring committee monitored the trial and reviewed data at the first interim analysis for safety (321 participants followed

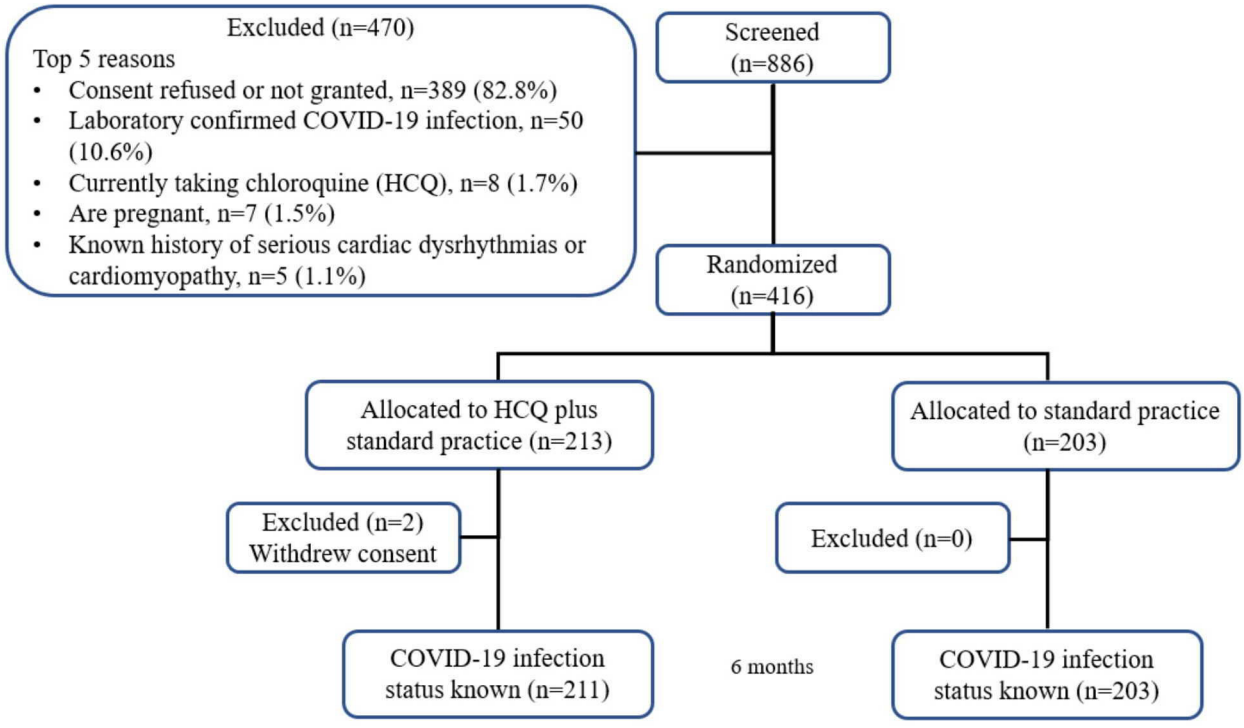

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1 Baseline characteristics

Characteristics	Standard practice (PPE) (n=203)	HCQ +standard practice (PPE) (n=213)	Total (n=416)
Age (years)			
Mean (SD)	31.8 (8.63)	32.3 (9.65)	32.1 (9.16)
Median (Q1; Q3)	29.0 (25.0; 36.0)	30.0 (25.0; 38.0)	30.0 (25.0; 37.0)
Sex (%)			
Male	106 (52.2)	113 (53.1)	219 (52.6)
Female	97 (47.8)	100 (46.9)	197 (47.4)
Role (%)			
Nurse	68 (33.5)	67 (31.5)	135 (32.5)
Doctor	31 (15.3)	34 (16.0)	65 (15.6)
Allied health worker	44 (21.7)	46 (21.6)	90 (21.6)
Ancillary worker	60 (29.6)	66 (31.0)	126 (30.3)
Visiting doctor	0 (0.0)	0 (0.0)	0 (0.0)
Usual place of work (%)			
ICU	53 (26.1)	53 (24.9)	106 (25.5)
Emergency department	18 (8.9)	26 (12.2)	44 (10.6)
Ward	130 (64.0)	130 (61.0)	260 (62.5)
Outpatient	2 (1.0)	4 (1.9)	6 (1.4)
Weight (kg)			
Mean (SD)	61.7 (13.15)	62.3 (14.02)	62.0 (13.59)
Median (Q1; Q3)	60.0 (52.0; 70.0)	61.0 (52.0; 70.0)	61.0 (52.0; 70.0)
Height (cm)			
Mean (SD)	161.7 (12.15)	161.7 (9.90)	161.7 (11.04)
Median (Q1; Q3)	162.0 (155.0; 169.0)	161.0 (155.0; 169.0)	161.0 (155.0; 169.0)
Smoker (%)			
No	194 (95.6)	205 (96.2)	399 (95.9)
Yes	9 (4.4)	8 (3.8)	17 (4.1)
Diabetes (%)			
No	200 (98.5)	206 (96.7)	406 (97.6)
Yes	3 (1.5)	7 (3.3)	10 (2.4)
High blood pressure or taking blood pressure medication (%)			
No	200 (98.5)	211 (99.1)	411 (98.8)
Yes	3 (1.5)	2 (0.9)	5 (1.2)
Chronic heart disease (%)			
No	203 (100)	213 (100)	416 (100)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Chronic lung disease (%)			
No	203 (100)	213 (100)	416 (100)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Chronic kidney disease (%)			
No	203 (100)	211 (99.1)	414 (99.5)
Yes	0 (0.0)	2 (0.9)	2 (0.5)
Chronic liver disease (%)			
No	203 (100)	213 (100)	416 (100)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
BCG (TB, tuberculosis) vaccination during childhood (%)			
No	25 (12.3)	35 (16.4)	60 (14.4)

Continued

Table 1 Continued

Characteristics	Standard practice (PPE) (n=203)	HCQ +standard practice (PPE) (n=213)	Total (n=416)
Yes	152 (74.9)	151 (70.9)	303 (72.8)
Unknown	26 (12.8)	27 (12.7)	53 (12.7)
Use of any PPE during last contact with patient with suspected or confirmed COVID-19 (%)			
No	0 (0.0)	0 (0.0)	0 (0.0)
Yes	203 (100)	213 (100)	416 (100)

HCQ, hydroxychloroquine; ICU, intensive care unit; PPE, personal protective equipment.

up for 4 weeks). The trial was stopped on 4 February 2021 after the first interim analysis because of slow enrolment due to the commencement of the vaccination programme and a high likelihood of futility (online supplemental appendix page 7); by this time, 416 participants had been randomised and the enrolled participants were followed up for the full 6-month duration. The trial was conducted in accordance with ethical principles consistent with the Declaration of Helsinki,[15] the ICH Good Clinical Practice guidelines[16] and all other relevant national and regional guidelines. The trial was sponsored by The George Institute for Global Health.

The trial protocol (online supplemental appendix)[17] and statistical analysis plan (online supplemental appendix)[18] were published a priori. All the authors vouch for the adherence to the protocol, for the accuracy and completeness of data and for the reporting of serious adverse events.

Participants

All HCWs (medical, nursing, allied health and ancillary workers) working in an environment with direct exposure to patients with confirmed COVID-19 infection and providing written informed consent were eligible for enrolment. Direct exposure to COVID-19 was defined as participants working in the areas designated for care of patients with COVID-19 in the hospitals (emergency room, wards, intensive care units (ICU)). We excluded those that did not provide consent, had a history of laboratory-confirmed COVID-19 infection, were already on HCQ, or pregnant or breast feeding. The full list of exclusion criteria is provided in the online supplemental appendix page 4.

Randomisation and masking

We used centralised randomisation and a computer-generated allocation sequence with permuted blocks of varying sizes. Randomisation was stratified by site and by role of HCW (nurse, doctor and other). This was an unblinded study.

Trial procedures

Participants were randomised in a 1:1 ratio to receive either HCQ plus PPE or PPE alone. In the HCQ group, in addition to use of PPE, HCWs received 400 mg of HCQ twice on the day of enrolment, followed by 400 mg once a week for a total of 12 weeks. This dose was chosen based on the recommendation issued by ICMR. All the HCWs in this arm underwent an ECG between weeks 4 and 6 and asked to report any side effects such as chest pain, palpitations or syncope.

HCWs were advised to stop the drug if they contracted COVID-19 during the intervention period, if they developed any serious adverse reactions to HCQ or if they no longer desired to continue in the trial. The trial drug would also be stopped if the corrected QT interval in the mid-trial ECG exceeded 450 ms irrespective of symptoms. For HCWs wishing to stop the drug during the intervention period, consent was sought for collecting follow-up data.

HCWs randomised to PPE alone group were asked to continue using appropriate PPE as per their institutional recommendations. They were discouraged from taking HCQ and intake of HCQ in this group was considered a protocol violation. ECG was performed in this arm only if the participant reported symptoms such as chest pain, palpitations or syncope.

Outcomes

The primary outcome was the proportion of laboratory-confirmed (by reverse transcriptase PCR or presence of antibodies) SARS-CoV-2 infection in the 6 months after randomisation. Secondary outcomes included hospitalisation due to suspected or confirmed COVID-19 infection, need for ICU or high dependency unit (HDU) admission, all-cause mortality, need for respiratory support (including O_2 therapy, non-invasive and invasive ventilation), need for kidney replacement therapy, need for vasopressors, hospital length of stay, ICU or HDU length of stay, readmission to hospital and days absent from work due to suspected or confirmed COVID-19 infection.

Data collection

Baseline data included designation of the HCW, role in the COVID-19 ward or ICU, demographics, average shift duration and comorbidities. Weekly follow-up was performed for all participants using a questionnaire either in person or over the phone. Information collected during follow-up included exposure during the week, compliance with the protocol and adverse events, if any. For the primary outcome, participants shared a copy of the laboratory report confirming the presence of COVID-19 infection. Data on hospitalisation and related

Table 2 Primary outcome and dichotomous secondary outcomes

Outcome	Standard practice (PPE) (n=203)	HCQ +standard practice (PPE) (n=211)	Unadjusted		Adjusted*			
			OR (95% CI)	P value†	OR (95% CI)	P value	Risk difference (95% CI)	P value
Laboratory-confirmed COVID-19 infection within 6 months after randomisation (primary outcome)	12 (5.9%)	11 (5.2%)	0.88 (0.38 to 2.03)	0.83	0.85 (0.35 to 2.07)	0.72	–0.7% (–7.8% to 6.4%)	0.95
Secondary outcomes								
Laboratory-confirmed or suspected‡ COVID-19 infection within 6 months after randomisation	12 (5.9%)	12 (5.7%)	0.96 (0.42 to 2.19)	1.00	0.94 (0.39 to 2.24)	0.89	–0.3% (–7.5% to 6.9%)	0.98
Hospitalised due to suspected COVID-19	2 (0.9%)	1 (0.5%)	0.48 (0.04 to 5.32)	0.62	NA		NA	
Admitted to ICU or HDU due to suspected COVID-19	0 (0.0%)	1 (0.5%)	NA	1.00	NA		NA	
Death from any cause	0 (0.0%)	0 (0.0%)			NA		NA	
Need for O_2 supplementation or ventilation:								
Oxygen supplementation	1 (0.5%)	1(0.5%)	0.96(0.06, 15.48)	1.00	NA		NA	
Ventilation	0 (0.0%)	0 (0.0%)	NA	NA	NA		NA	
Need for vasopressors	0 (0.0%)	0 (0.0%)	NA	NA	NA		NA	
Need for renal replacement therapy	0 (0.0%)	0 (0.0%)	NA	NA	NA		NA	
Readmission to hospital	0 (0.0%)	0 (0.0%)	NA	NA	NA		NA	

*Adjusted for role of HCW (fixed effect) and site (random effect).
†Fisher's exact test p value.
‡Defined as symptoms with more than 10 days off work.
HCQ, hydroxychloroquine; HCW, healthcare worker; HDU, high dependency unit; ICU, intensive care unit; NA, not applicable; PPE, personal protective equipment.

secondary outcomes were obtained from the medical records. Both groups were followed up for a total of 25 weeks from randomisation.

Statistical analysis

We estimated that the enrolment of 6950 HCWs would give us a power of 80% to detect a 25% relative reduction in the proportion of confirmed COVID-19 infections from an estimated baseline proportion of 10% and a two-sided alpha of 5%. This sample size allowed for a potential loss to follow-up of 10% and a potential non-compliance rate of 10%.

Analysis of the primary and secondary outcomes was performed in the intention-to-treat population, which included all those that were randomised. In the event that consent was withdrawn, data were included only if the participant explicitly agreed for her/his data to be used until the point she/he revoked consent.

Discrete variables are summarised as percentages and frequencies. Continuous variables are summarised as mean and SD or median and IQR. The primary outcome is analysed without imputation of missing data. To account for the stratification by site and HCW role and maximise power, the main analysis was performed using logistic regression with treatment allocation and HCW role as fixed effects and site as a random effect. The effect of the intervention is presented as OR and corresponding 95% CIs. For ease of interpretation, risk difference and 95% CI are also presented. Given the overall small number of events, no adjustment for other covariates was performed. Crude proportions by treatment arm are also reported with an unadjusted OR, 95% CIs and a Fisher's exact test p value.

For the dichotomous secondary outcomes, comparison of proportions is summarised by treatment arm and compared using logistic regression (similar to the primary analysis). For the continuous outcomes, hospital and ICU length of stay are analysed as the number of days alive and free of outcome. Days alive and free of outcome were censored at 175 days after randomisation calculated between randomisation and end of week 25 and will therefore have values between 0 and 175 days. These are summarised as means and SDs (or medians and quartiles) and compared between the two arms using a Mann-Whitney U test. The number of hospitalisations, ICU admissions and days off work due to COVID-19 infection were very few, hence regressions outlined in the statistical analysis plan were not carried out.

Four prespecified subgroup analyses were included based on age (>35 or ≤35 years), sex (male vs female), role of HCW (doctor vs nurse vs other) and BCG vaccination status (yes vs no). The analysis for each subgroup, except for role of HCW, was performed by adding the subgroup variables as well as its interaction with the intervention as fixed effects to the main logistic regression model.

Adverse events deemed possibly, probably or definitely related to study treatment were summarised as the number and proportion of participants experiencing at least one event and by category of events and overall number of events. Proportion of participants with adverse events was compared between the two treatment arms using the Fisher's exact test, both overall and by category.

Patient and public involvement

There was no direct patient or public involvement in the conception or design of this trial.

RESULTS

Between 29 June 2020 and 4 February 2021, a total of 886 eligible HCWs were screened; 416 were randomised. Two hundred and thirteen participants were randomly allocated to HCQ plus PPE and 203 to standard PPE alone. Figure 1 shows the flow of participants in the trial. Information on trial sites and number of participants enrolled by site is provided in online supplemental table 1. All participants were followed up to 6 months with the last date of follow-up as 29 July 2021. Of the 416 participants, two were lost to follow-up and 414 were included for the analysis of the primary and key secondary outcomes.

The baseline characteristics of the included participants were comparable between the two groups (table 1 and online supplemental table 7). Participants were young (mean age 32.1, SD 9.1) and healthy with low-comorbid burden. About 32.5% of the participants were nurses, 30.3% ancillary HCWs, 21.6% allied health workers and 15.6% doctors; 47.4% were female. Approximately 63% of the participants were enrolled from COVID-19 wards, 26% from ICU and 10% from the emergency room.

Vaccination started in India on 16 January 2021 and details of vaccination status of the participants are provided in online supplemental table 8.

Trial intervention

Compliance with the intervention was high (87.4%) with a total of 312 HCQ doses being missed out of the 2483 recorded doses. Details are provided in online supplemental tables 2 and 3.

Outcomes

Primary outcome

In the 6 months after randomisation, 11 participants assigned to the HCQ (8 confirmed by PCR and 3 by antibody test) and 12 participants assigned to the PPE only (10 confirmed by PCR and 2 by antibody test) groups met the primary end point of laboratory-confirmed COVID-19 (5.2% vs 5.9%; OR 0.85, 95% CI 0.35 to 2.07, p=0.72) (table 2). There was no significant heterogeneity in the effect of the intervention on the primary outcome in the four prespecified subgroups (figure 2).

Secondary outcomes

There were no significant differences between the intervention and control arms with respect to the key secondary outcomes (table 2 and online supplemental table 4). Three participants needed hospitalisation (two in the control and one in the intervention arm) and one

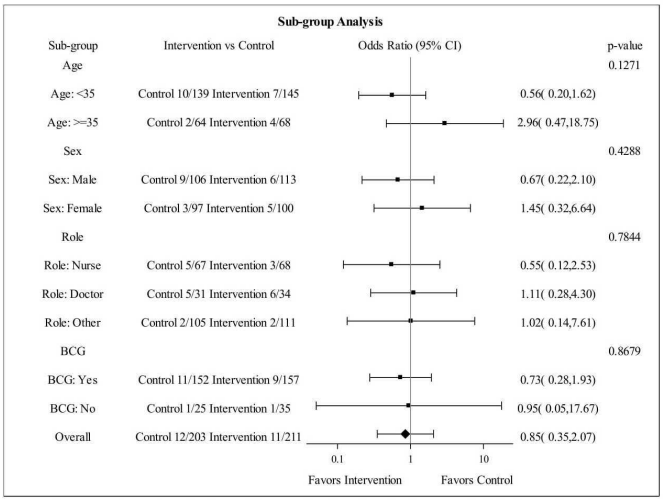

Figure 2 Forest plot for subgroup analysis of laboratory-confirmed COVID-19 infection within 6 months after randomisation. Intervention versus control: number of patients with events/total number of patients, p value is for interaction effect.

participant in either group needed supplemental oxygen therapy. There were no deaths.

Adverse events

The proportions of adverse events were 9.9% and 6.9% in the HCQ and PPE groups, respectively (risk ratio 1.43; 95% CI 0.61 to 2.23, p=0.29); all were minor and there were no serious adverse events (table 3 and online supplemental tables 5 and 6). ECG was performed in 172 of the 213 participants randomised to the HCQ arm and there were two participants with ECG evidence of QTc prolongation (more than 450 ms). In both these participants, the trial drug was stopped without any further adverse events.

DISCUSSION

In this trial evaluating HCQ prophylaxis among HCWs in India, the use of HCQ in addition to PPE did not result in a lower incidence of laboratory-confirmed COVID-19 as compared with PPE alone. This effect did not differ in any of the prespecified subgroups. There were also no between-group differences in any of the key secondary outcomes. There was no statistically significant difference in the proportion of adverse events between the two groups and there were no serious adverse events.

The results of our trial are consistent with previously published data from other settings. Nine published trials[19–27] have so far evaluated the role of HCQ as a prophylactic agent. Of these, four evaluated the role of HCQ as a postexposure prophylaxis agent among contacts of patients with COVID-19,[19–22] one evaluated the drug among migrant workers[23] and four among HCWs.[24–27]

Rajasingham *et al*[24] conducted a three-arm, parallel-group trial comparing two dosing regimens of HCQ versus a placebo (n=1483). Neither of the dosing regimens were effective in reducing the primary outcome of COVID-19-free survival time. In contrast to HOPE, the primary outcome was a combination of laboratory-confirmed and

Table 3 Adverse events

Characteristics	PPE only (n=203)	HCQ+PPE (n=213)	Total (n=416)	P value*	Risk ratio (95% CI)
Adverse event				0.29	
No	189 (93.1%)	192 (90.1%)	381 (91.6%)		
Yes	14 (6.9%)	21 (9.9%)	35 (8.4%)		1.43 (0.61 to 2.23)
Serious adverse event					
No	203/203 (100%)	213/213 (100%)	416/416 (100%)		
Resulted in death					
No	203/203 (100%)	213/213 (100%)	416/416 (100%)		
Life threatening					
No	203/203 (100%)	213/213 (100%)	416/416 (100%)		
Requires prolonged hospitalisation					
No	203/203 (100%)	213/213 (100%)	416/416 (100%)		
Results in persistent or severe disability/incapacity					
No	203/203 (100%)	213/213 (100%)	416/416 (100%)		
Results in congenital anomaly/birth defect					
No	203/203 (100%)	213/213 (100%)	416/416 (100%)		
Is medically significant to qualify as a serious event					
No	203/203 (100%)	213/213 (100%)	416/416 (100%)		

*Fisher's exact test
HCQ, hydroxychloroquine; PPE, personal protective equipment.

probable COVID-19 (by symptoms). Additionally, participants in the trial were enrolled through approaches on social media and not through a systematic strategy of hospital or site-level screening.

In another trial evaluating HCQ as pre-exposure prophylaxis, Abella and colleagues[25] randomised 132 participants. The dosing regimen in this trial was 600 mg of oral HCQ or placebo daily for a period of 8 weeks. The trial included participants with a negative PCR at baseline and retested at 4 and 8 weeks. The trial was stopped after 132 participants were enrolled (planned n=200) due to low event rates and a signal for futility.

Two other trials evaluating the role of HCQ among HCWs have been published as preprints.[26 27] In a single-centre placebo-controlled trial from Mexico, investigators enrolled 130 participants and found no difference in the primary outcome. In another phase II trial from Pakistan, the investigators enrolled 200 participants into one of four arms—three treatment arms with different dosages of HCQ and one control arm. Participants were followed up to 12 weeks and the study found no difference in the rate of COVID-19 positivity.

To date, none of the trials have provided a definitive answer on the effectiveness of HCQ as a prophylactic agent. Based on the observed event rate at the interim analysis of HOPE, the Data Safety Monitoring Committee estimated that 10 000 participants would be needed in each arm to have a 90% power to detect a 30% relative reduction in the primary outcome. Based on these numbers, the availability of vaccines and the perceived loss of clinical equipoise, the question on the effectiveness of HCQ as prophylaxis is likely to remain unanswered.

Our trial has important strengths. HOPE is the largest multicentre trial of HCQ prophylaxis from a lower middle-income country. A high proportion of eligible HCWs received the trial intervention as planned, very few enrolled participants were lost to follow-up and we incorporated a mid-trial ECG in the HCQ arm for safety. Most participating centres had limited formal research infrastructure or experience and HOPE served to create research capacity at these sites. Our trial was conducted to the highest methodological standards, was overseen by a trial steering committee and supervised by an independent data monitoring committee. We had prespecified stopping rules for harm and our trial protocol and statistical analysis plan were published a priori. We had high compliance with the treatment protocol, 99.3% follow-up for the primary outcome and the longest follow-up period among HCQ prophylaxis trials. Our trial had nearly equal proportions of men and women and was diverse in its inclusion of different HCW roles, thereby enhancing generalisability.

Our trial had limitations. Given the slow enrolment, the declining enthusiasm for HCQ and the roll-out of vaccination, we were unable to complete the trial to the planned sample size and hence were underpowered at the time of stopping. We did not include a placebo arm or employ blinding; however, bias was mitigated by the choice of an objective primary end point. We did not perform a baseline PCR or antibody testing and relied on participant history to rule out prior COVID-19. Our screening to randomisation ratio of 0.46 is on the lower side with refusal of consent being the main reason for non-inclusion.

In conclusion, HCQ in addition to PPE was not associated with a lower incidence of COVID-19 as compared with PPE alone. However definitive inferences are precluded by the limited statistical power.

Author affiliations
[1]Critical Care, Apollo Hospitals, Chennai, Tamil Nadu, India
[2]The George Institute for Global Health, New Delhi, Delhi, India
[3]The George Institute for Global Health, Newtown, New South Wales, Australia
[4]Homi Bhabha National Institute, Mumbai, Maharashtra, India
[5]Anaesthesiology and Critical Care Medicine, Tata Memorial Hospital, Mumbai, India
[6]Critical Care, The George Institute for Global Health, Newtown, New South Wales, Australia
[7]University of New South Wales, Sydney, New South Wales, Australia
[8]Kasturba Medical College, Manipal, Karnataka, India
[9]Aligarh Muslim University, Aligarh, Uttar Pradesh, India
[10]Apollo Hospitals Ahmedabad, Ahmedabad, Gujarat, India
[11]Christian Hospital, Nabarangpur, Odisha, India
[12]Apollo Hospitals, Madurai, Tamil Nadu, India
[13]Indraprastha Apollo Hospital, New Delhi, Delhi, India
[14]NephroPlus Health Services, Hyderabad, Telangana, India
[15]Wesley Hospital, Brisbane, Queensland, Australia
[16]Wesley Medical Research, Brisbane, Queensland, Australia

Twitter Bharath Kumar Tirupakuzhi Vijayaraghavan @bharathkumartv, Vivekanand Jha @vjha126, Dorrilyn Rajbhandari @DorrilynR, Sheila Nainan Myatra @SheilaMyatra, Lachlan Hugh Donaldson @lhdonaldson, Naomi E Hammond @naomihammond and Rohina Joshi @rohinajoshi

Collaborators Sponsor: The George Institute for Global Health, India. Management committee: Vivekanand Jha, Bharath Kumar Tirupakuzhi Vijayaraghavan, Balasubramanian Venkatesh (chair), Arpita Ghosh, Oommen John, Sheila Myatra, Rohina Joshi, Naomi Hammond, Lachlan Donaldson, Dorrilyn Rajbhandari, Sumaiya Arfin, Abhinav Bassi. Independent data monitoring and safety committee: Rinaldo Bellomo (chair), Jeyaraj Pandian, Niveditha Devasenapathy, Amritendu Battacharya (statistician). Funding body: Wesley Medical Research, Australia. Site investigators and research staff (site personnel are listed in alphabetical order). Sites were chosen based on them being identified as COVID hospitals by the Government of India or by virtue of them treating patients with COVID-19. The primary investigator at each site is marked with asterisk (*). Critical Care Consultants Group, Apollo Hospitals, Chennai: Bharath Kumar Tirupakuzhi Vijayaraghavan*, Pavan Kumar Vecham, Evangeline Elvira, Gomathi Parthasarathy, Archana Ragunathan, Gnanavel Rajendra Kunjurao, Pavithra Sampath Kumar, Hilda Nirmala Kumari, Jayanthi Swaminathan, Murshid Cheriyeri Peediyekkal, Arun Chander Yadav; Department of Medicine, Kasturba Medical College, Manipal: Aarthi Venkatramanan, Cynthia Amrutha Sukumar*, Dharini Prasad, Krishnanda Nayak, Ravindra Prabhu, Rohini Bilagi, Sudha Vidyasagar; Department of Cardiology, Apollo Hospitals International, Ahmedabad: Akash Bhange, Ashwani Kumar, Bhumika Patel, Chirag Patel, Ekta Ramchandani, Jinesh Patel, Krupa Gandhi, Subir Ghosh*; Department of Internal Medicine, Apollo Health City, Jubilee Hills, Hyderabad: N Prathyusha, Rajib Paul*; Department of Infectious Diseases, Apollo Hospitals, Madurai: Rayshma Rao Bonshlay Lakshmanan, S Hari Krishnan*, S Radhakrishnan; Department of Medicine, Christian Hospital, Nabarangpur: Abhishek George Mehta, Michael John, Mousumi Pradhan, Santosh Kumar Nag*; Department of Medicine, Jawahar Lal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh: Syed Haider Mehdi Husaini*; Department of Radiotherapy: Shahid Ali Siddique; District Early Intervention Centre (DEIC-COE, RBSK): Md Naved ur Rahman; Office of Principal: Mohammad Jamalludeen; NephroPlus Dialysis Centres, Hyderabad, India: Mounika Amarneni, Kamal D Shah*, Suresh Sankar, Vidya Rajesh Joshi; Department of Pulmonary Medicine and Critical Care, Indraprastha Apollo Hospital, New Delhi: Alka Yadav, Nikhil Modi, Rinku Dahiya, Viny Kantroo*, Vijay Kumar; The George Institute for Global Health, India and Australia: Dorrilyn Rajbhandari (senior project manager), Abhinav Bassi, Sumaiya Arfin (project managers); Critical Care Division (Academics),

India: Arpita Ghosh, Vivekanand Jha, Oommen John, Bharath Kumar Tirupakuzhi Vijayaraghavan; Australia: Lachlan Donaldson, Naomi Hammond, Rohina Joshi, Serena Knowles, Balasubramanian Venkatesh. Clinical research associates and clinical trial assistants, India: Nikita Bathla, Rajesh Joshi, Mallikarjuna Kunigari; Australia: Fatima Butt. Data management, Australia: Serena Knowles, Conrad Nangla.

Contributors BKTV: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing—original draft, writing—review and editing. VJ: conceptualisation, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, writing—review and editing. DR, SA, AB: data curation, project administration, resources, software, validation, writing—review and editing. SNM: investigation, supervision, writing—review and editing. AG, AB: data curation, formal analysis, validation, visualisation, writing—original draft, writing—review and editing. LHD: methodology, supervision, writing—review and editing. NEH: methodology, project administration, resources, supervision, writing—review and editing. OJ: investigation, methodology, supervision, writing—review and editing. RJ: supervision, writing—review and editing. MK: project administration, resources, writing—review and editing. CA, SHMH, SG, SKN, HKS, VK, KDS: investigation, writing—review and editing. BV: conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, writing—original draft, writing—review and editing. BKTV acts as the guarantor.

Funding The trial was funded by Wesley Medical Research, Australia (grant number: 2020-02).

Disclaimer The funder had no role in the conception, design, conduct, analysis or the decision to publish.

Competing interests OJ reports being a member of the WHO R&D Blueprint Safety Monitoring Team, ACT Accelerator—R&D Digital Health working group and COVID-19 Clinical Research Coalition data sharing working group.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by The George Institute Ethics Committee (reference number: 08-2020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified patient data will be made available beginning 6 months after publication of the study and ending at 2 years. All requests for data sharing must be accompanied by a formal request, a study proposal with clear statement of aims and hypotheses and a statistical analysis plan. All applications will be assessed by the HOPE Management Committee. Applications from investigators with suitable academic capability to conduct the proposed work will be given consideration. Any proposal will require approval from the ethics committee which approved the conduct of this trial prior to sharing of any patient data. If a proposal is approved, a signed data transfer agreement will be required before data sharing.

ORCID iDs
Bharath Kumar Tirupakuzhi Vijayaraghavan http://orcid.org/0000-0002-1801-0667
Arpita Ghosh http://orcid.org/0000-0003-0036-4376
Naomi E Hammond http://orcid.org/0000-0002-6559-7747

REFERENCES

1 WHO, 2021. Available: https://covid19.who.int/ [Accessed 13 Sep 2021].
2 WHO, 2021. Available: https://covid19.who.int/region/searo/country/in [Accessed 13 Sep 2021].
3 WHO, 2021. Available: https://www.who.int/csr/sars/country/table2004_04_21/en/ [Accessed 13 Sep 2021].
4 WHO, 2021. Available: http://applications.emro.who.int/docs/EMCSR246E.pdf?ua=1 [Accessed 13 Sep 2021].
5 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019. *JAMA* 2020.
6 Epicentro, 2021. Available: https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati [Accessed 13 Sep 2021].
7 Gómez-Ochoa SA, Franco OH, Rojas LZ, *et al*. COVID-19 in health-care workers: a living systematic review and meta-analysis of prevalence, risk factors, clinical characteristics, and outcomes. *Am J Epidemiol* 2021;190:161–75.
8 Liu J, Cao R, Xu M, *et al*. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020;6:16.
9 Vincent MJ, Bergeron E, Benjannet S, *et al*. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* 2005;2:69.
10 FDA, 2021. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf [Accessed 13 Sep 2021].
11 Ruiz S, Concordet D, Lanot T, *et al*. Hydroxychloroquine lung pharmacokinetics in critically ill patients with COVID-19. *Int J Antimicrob Agents* 2021;57:106247.
12 Rowland Yeo K, Zhang M, Pan X, *et al*. Impact of disease on plasma and lung exposure of chloroquine, hydroxychloroquine and azithromycin: application of PBPK modeling. *Clin Pharmacol Ther* 2020;108:976–84.
13 MOHFW, 2021. Available: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf [Accessed 13 Sep 2021].
14 DAIC, 2021. Available: https://www.dicardiology.com/article/fda-reports-deaths-and-injuries-use-antimalarial-hydroxychloroquine-covid-19-patients [Accessed 13 Sep 2021].
15 WMA, 2021. Available: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ [Accessed 13 Sep 2021].
16 ICH, 2021. Available: https://www.ich.org/page/efficacy-guidelines [Accessed 13 Sep 2021].
17 Tirupakuzhi Vijayaraghavan BK, Jha V, Rajbhandari D, *et al*. Hydroxychloroquine plus personal protective equipment versus standard personal protective equipment alone for the prevention of COVID-19 infections among frontline healthcare workers: the HydrOxychloroquine Prophylaxis Evaluation(HOPE) trial: A structured summary of a study protocol for a randomized controlled trial. *Trials* 2020;21:754.
18 Ghosh A, Bhattacharya A, Jha V. *Statistical analysis plan for the HydrOxychloroquine prophylaxis evaluation(HOPE) trial*, 2021.
19 Boulware DR, Pullen MF, Bangdiwala AS, *et al*. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med Overseas Ed* 2020;383:517–25.
20 Mitjà O, Corbacho-Monné M, Ubals M, *et al*. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. *N Engl J Med* 2021;384:417–27.
21 Dhibar DP, Arora N, Kakkar A, *et al*. Post-exposure prophylaxis with hydroxychloroquine for the prevention of COVID-19, a myth or a reality? the PEP-CQ study. *Int J Antimicrob Agents* 2020;56:106224.
22 Barnabas RV, Brown ER, Bershteyn A. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection. *Ann Intern Med* 2021.
23 Seet RCS, Quek AML, Ooi DSQ, *et al*. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: an open-label randomized trial. *Int J Infect Dis* 2021;106:314–22.
24 Rajasingham R, Bangdiwala AS, Nicol MR, *et al*. Hydroxychloroquine as pre-exposure prophylaxis for coronavirus disease 2019 (COVID-19) in healthcare workers: a randomized trial. *Clin Infect Dis* 2021;72:e835–43.
25 Abella BS, Jolkovsky EL, Biney BT, *et al*. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med* 2021;181:195–202.
26 Rojas-Serrano J, Ireri AMP, Vazquez-Perez J. Hydroxychloroquine for prophylaxis of COVID-19 in health workers: a randomized clinical trial. *medRxiv*.

27 Syed F, Arif MA, Niazi R. Pre-Exposure prophylaxis with various doses of hydroxychloroquine among high-risk COVID-19 healthcare personnel: CHEER randomized controlled trial. *medRxiv*.