BMJ Open

Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomised clinical trials

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To cite: Hong H, Friedland A, Hu M, *et al*. Safety and efficacy of hydroxychloroquine as prophylactic against COVID-19 in healthcare workers: a meta-analysis of randomised clinical trials. *BMJ Open* 2023;**13**:e065305. doi:10.1136/bmjopen-2022-065305

► 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-2022-065305).

Received 02 June 2022
Accepted 31 May 2023

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ABSTRACT

Objective We studied the safety and efficacy of hydroxychloroquine (HCQ) as pre-exposure prophylaxis for COVID-19 in healthcare workers (HCWs), using a meta-analysis of randomised controlled trials (RCTs).

Data sources PubMed and EMBASE databases were searched to identify randomised trials studying HCQ.

Study selection Ten RCTs were identified (n=5079 participants).

Data extraction and synthesis The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used in this systematic review and meta-analysis between HCQ and placebo using a Bayesian random-effects model. A pre-hoc statistical analysis plan was written.

Main outcomes The primary efficacy outcome was PCR-confirmed SARS-CoV-2 infection and the primary safety outcome was incidence of adverse events. The secondary outcome included clinically suspected SARS-CoV-2 infection.

Results Compared with placebo, HCWs randomised to HCQ had no significant difference in PCR-confirmed SARS-CoV-2 infection (OR 0.92, 95% credible interval (CI): 0.58, 1.37) or clinically suspected SARS-CoV-2 infection (OR 0.78, 95% CI: 0.57, 1.10), but significant difference in adverse events (OR 1.35, 95% CI: 1.03, 1.73).

Conclusions and relevance Our meta-analysis of 10 RCTs investigating the safety and efficacy of HCQ as pre-exposure prophylaxis in HCWs found that compared with placebo, HCQ does not significantly reduce the risk of confirmed or clinically suspected SARS-CoV-2 infection, while HCQ significantly increases adverse events.

PROSPERO registration number CRD42021285093.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Bayesian meta-analysis models with random effects fitted the data.
⇒ The 10 trials included in the meta-analysis represent wide geographical locations including the USA, Canada, Mexico, India, Spain, Bolivia, Venezuela, Peru and Pakistan.
⇒ The findings can be applied to healthcare workers but should not be generalised to a broader population.

INTRODUCTION

Early during the SARS-CoV-2 pandemic, based on in vitro antiviral activity of both chloroquine and hydroxychloroquine (HCQ) against SARS-CoV-2,[1–3] clinicians considered use of HCQ for treatment and prevention of SARS-CoV-2 infection and the associated disease, COVID-19. While there are now published randomised controlled trials (RCTs) of HCQ for the treatment of COVID-19 in the inpatient and outpatient setting,[4 5] there remains a lack of adequately powered RCTs of HCQ for the pre-exposure prophylaxis (PrEP) of SARS-CoV-2 infection. A number of COVID-19 clinical studies including PrEP studies were planned early in the pandemic; however, several never opened to enrolment and those that did open were closed early without reaching full accrual due to the rapidly changing landscape of preventative therapies, including vaccines, and a significant shift in public opinion of HCQ as a medical intervention for SARS-CoV-2.[6]

Vaccination access remains insufficient globally.[7] Specifically, in low-income countries, only 33% of healthcare workers (HCWs) are fully vaccinated. While high-income countries have better coverage, overall, 38% of countries did not achieve the milestone of 70% vaccination coverage for HCWs by

the end of 2021.[8] Thus, studying the PrEP potential for a drug with a known safety profile is crucial to protect people at high risk of exposures, such as HCWs.[9 10] Two large randomised, placebo-controlled trials testing the safety and efficacy of HCQ as PrEP for COVID-19 in HCWs[11 12] showed potential for a modest benefit of HCQ but were both underpowered, if a modest effect exists. More trials[13–15] studying HCQ as PrEP of COVID-19 in HCWs have been published with similar limitations.

To address the most common limitation, inadequate power to show a modest effect, we conducted a formal meta-analysis of pre-exposure prophylactic HCQ studies in HCWs. We conducted a systematic search for clinical trials of pre-exposure prophylactic use of HCQ against infection of SARS-CoV-2 in HCWs, thoroughly compared similarities and differences in characteristics of the identified studies and performed a Bayesian meta-analysis to combine results of the trials.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used in this systematic review and meta-analysis.[16] A statistical analysis plan was written in advance and the review protocol was registered at PROSPERO (CRD42021285093).

Search strategy and information sources

We searched PubMed/Medline and Ovid/EMBASE databases from database inception through the final search date, 14 March 2023. We used keywords related to COVID-19, HCQ and RCTs. The full search strategies are provided in online supplemental table 1.

Eligibility criteria and study selection

The eligibility criteria included phase II or phase III RCTs of HCQ for use as PrEP in HCWs with moderate to high risk of exposure. We excluded observational studies, crossover trials, studies where the method of allocation to treatment was not truly random, duplicate studies and non-original data studies. No language, publication date or publication status restrictions were applied. References of prior systematic reviews and meta-analyses were also screened for related studies. Study selection involved screening of titles and abstracts followed by full-text evaluation of possible eligible studies.

Data collection process

Each of the selected studies was independently reviewed by two reviewers (AF, MH or HH). We extracted data on the study design, baseline characteristics, interventions and outcomes. Any disagreements of collected information between reviews were reconciled through discussion by all three reviewers.

Outcome measures

The primary efficacy outcome for the meta-analysis was laboratory-confirmed SARS-CoV-2 infection by PCR test and the primary safety outcome was incidence of adverse events (table 1). The secondary efficacy outcome was suspected or probable SARS-CoV-2 infection. Included studies had the following outcome definitions: (1) laboratory-confirmed SARS-CoV-2 infection defined as COVID-19-like symptoms and positive SARS-CoV-2 PCR and (2) suspected or probable SARS-CoV-2 infection defined as COVID-19-like symptoms but lack of confirmatory PCR testing.

Treatment assignment

Our meta-analysis did not study HCQ dosing-specific effects. For studies randomising participants to more than one HCQ arm with different doses, all HCQ arms were merged and considered as a single HCQ arm. Such studies include the Rajasingham *et al*, McKinnon *et al* and Syed *et al* studies.[12 15 17]

Risk of bias and certainty of evidence assessment

Two independent reviewers (AF, HH) assessed the risk of bias (low, intermediate, high) of the included studies using the Cochrane's Collaboration tool[18] (online supplemental table 2). We assessed the certainty of evidence using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach.[19]

Statistical analysis

Bayesian logistic regression meta-analysis models under two assumptions (fixed effects and random effects) were fitted to estimate the OR of having an outcome between HCQ and placebo.[20] The fixed-effects model assumes that the OR is constant across studies, while the random-effects model accounts for heterogeneity in the ORs across studies. To assess and compare the goodness of fit of the fitted fixed-effects and random-effects models, we calculated the Watanabe-Akaike information criterion.[21] In the Bayesian models, we assigned non-informative prior distributions as no prior information was available. The ORs and the associated 95% credible intervals (CIs) were estimated using Markov chain Monte Carlo (MCMC) algorithms. In addition, we calculated Bayesian posterior probabilities of the OR smaller than 1 or 0.5 for the primary efficacy outcome, and greater than 2 for the safety outcome.[22] The SD of the random effects and I^2[23] were estimated to quantify the between-study heterogeneity, where small values of both metrics indicate slight heterogeneity. To identify publication bias, we plotted and assessed funnel plots for their symmetry and conducted the Egger's test.[24] All Bayesian meta-analyses were conducted using the rstan package (V.2.21.2)[25] in R V.4.0.2.[26] We used two parallel chains, where each chain consists of 50 000 samples after a 25 000-sample burn-in. We checked convergence of the MCMC chains for all model parameters using trace plots and Gelman-Rubin diagnostic statistics.[27]

Patient and public involvement

No patient involved.

Table 1 Treatment strategies, adherence, trial-defined primary outcome and study duration for trials included in the meta-analysis

	Trial-defined primary outcome	Study duration	Treatment group	Randomised treatment assignment	Randomised sample size
Naggie *et al*[13] (HERO-HCQ) NCT04334148	Confirmed (by NP swab PCR) or suspected COVID-19 infection through 30 days	60 days	HCQ	HCQ 600 mg two times per day loading dose for day 1, followed by 400 mg four times a day for 29 days	683
			Control	Placebo	676
Abella *et al*[11] (PATCH) NCT04329923	COVID-19 infection as determined by positive NP swab over 8 weeks	56 days (8 weeks)	HCQ	HCQ 600 mg daily for 60 days	64
			Control	Placebo	61
Rajasingham *et al*[12] (MN-COVID-PREP) NCT04328467	COVID-19-free survival time by lab-confirmed or probable illness	84 days (12 weeks)	HCQ*	HCQ loading doses (400 mg two times 6–8 hours apart), followed by 400 mg once weekly or 400 mg two times per week for 84 days	989
			Control	Placebo	494
Rojas-Serrano *et al*[14] NCT04318015	Time to symptomatic respiratory infection with a positive COVID-19 RT-PCR over 60 days	60 days	HCQ	HCQ 200 mg daily for 60 days	62
			Control	Placebo	65
McKinnon *et al*[15] (WHIP) NCT04341441	Lab-confirmed cases of COVID-19 determined by either IgM and IgG serology in blood sample or RT-PCR test results Confirmed new cases of COVID-19	56 days (8 weeks)	HCQ*	HCQ 400 mg loading dose for day 1, followed by 200 mg daily or 400 mg weekly on the same day of each week for 56 days	387
			Control	Placebo	191
Tirupakuzhi Vijayaraghavan *et al*[36] CTRI/2020/05/025067	Lab-confirmed SARS-CoV-2 infection by PCR or presence of antibodies	180 days (6 months)	HCQ	HCQ 400 mg two times on the day of enrolment, followed by 400 mg once a week for a total of 12 weeks plus personal protective equipment (PPE)	213
			Control	PPE	203
Polo *et al*[37] (EPICOS) NCT04334928	Lab-confirmed symptomatic COVID-19 by PCR	84 days (12 weeks)	HCQ†	HCQ 200 mg once daily	231
			Control	Placebo	223
Llanos-Cuentas *et al*[30] NCT04414241	COVID-19 cases confirmed by PCR or serological test	28 days (4 weeks)	HCQ	HCQ loading dose of 600 mg on the first day, followed by 400 mg every other day plus PPE	36
			Control	PPE	32
Grau-Pujol *et al*[38] NCT04331834	COVID-19-confirmed cases with seroconversion or PCR test	180 days (6 months)	HCQ	HCQ 400 mg daily for 4 consecutive days, followed by 400 mg weekly	142
			Control	Placebo	127
Syed *et al*[17] NCT04359537	COVID-19-free survival (COVID-19 confirmed by PCR)	84 days (12 weeks)	HCQ*	HCQ 400 mg two times for day 1, followed by 400 weekly or HCQ 400 mg once every 3 weeks or HCQ 200 mg once every 3 weeks	154
			Control	Placebo	46

*More than one HCQ group with different doses are lumped.
†The Polo *et al* study randomised participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.
HCQ, hydroxychloroquine; NP, nasopharyngeal; RT-PCR, reverse transcription PCR.

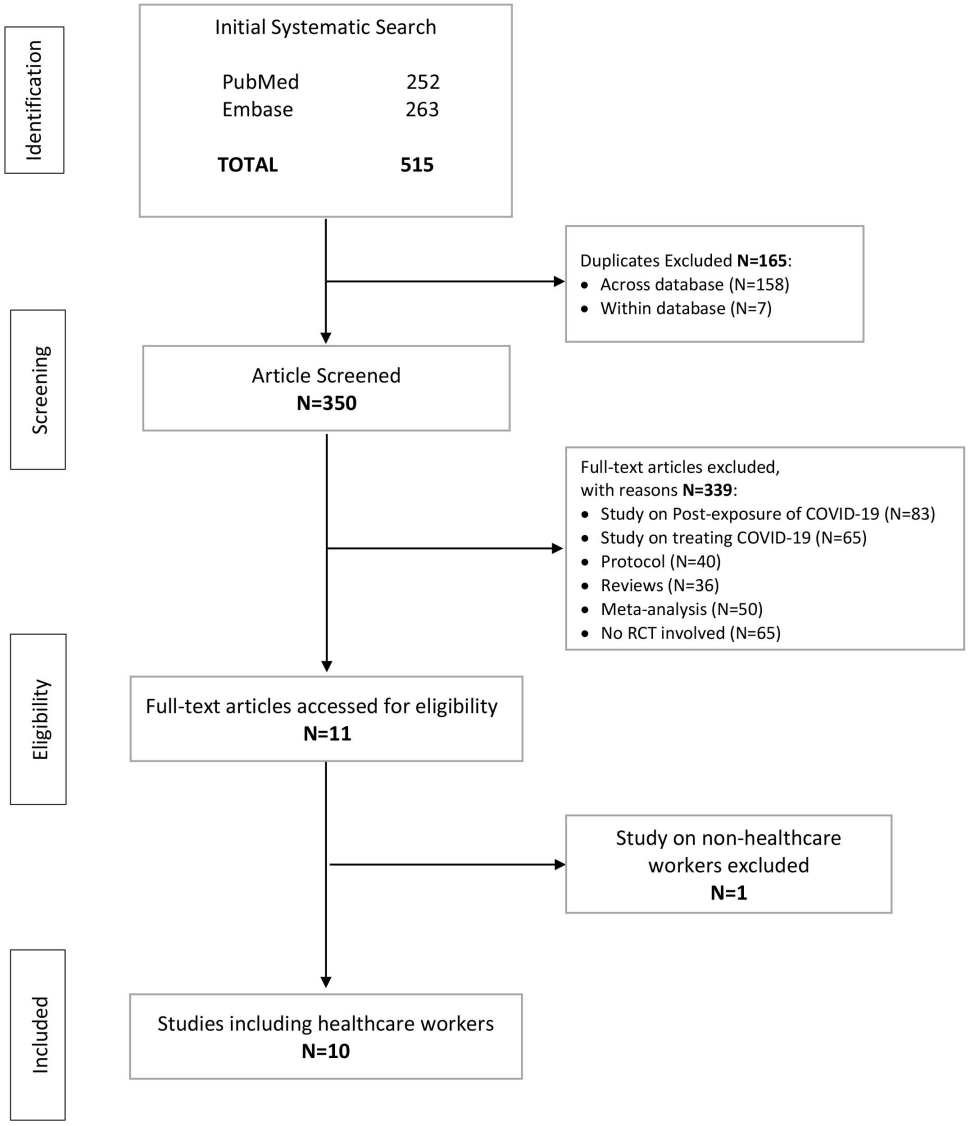

Figure 1 Flow chart of literature review. RCT, randomised controlled trial.

RESULTS

Search results

Our database search resulted in 350 unique studies after excluding duplicates. Of those, 339 studies were screened out due to irrelevance based on title and abstract screening. Eleven studies were assessed in full text for eligibility (figure 1). Of those, one trial was excluded from the meta-analysis because it studied with non-HCW populations. As a result, a total of 10 studies in a population consisting of HCWs were identified (table 1).

Study and patient characteristics

Study design, population, treatment strategies and key characteristics are presented in table 1 and online supplemental table 3. A total of 5079 randomised participants (2961 randomised to HCQ) from the 10 studies were included in the meta-analysis. The 10 studies defined HCWs broadly and included first responders (emergency medical services, fire and police). The follow-up duration of the 10 studies ranged from 28 days to 180 days. The HCQ dosing scheme varied across studies, including daily dosing ranging from 200 to 600 mg daily with or without a loading dose and once or two times a week or once every 3 weeks dosing. The duration of therapy also varied across studies (table 1). The trial-specific definitions of primary outcome and adverse events are comparable across trials (table 1 and online supplemental table 4).

Baseline characteristics by randomised treatment assignment are reported (online supplemental table 5). The average age ranged between 31 and 45 years. The aggregate proportion of women within each study varied across the 10 trials, with a range from 44% to 69%. In addition, the Abella *et al*[11] and Rojas-Serrano *et al*[14] studies had smaller sample size compared with the other three studies and showed a difference in female ratio between placebo and HCQ groups. In the Naggie *et al*,[13] Abella *et al*, Rajasingham *et al* and McKinnon *et al* studies, over 80% of study participants were white. The Abella *et al* and Rajasingham *et al* studies had high proportions of HCWs

working in an emergency department (56% and 41%, respectively), and the Abella *et al* study had a high proportion of nurses (67%).

Several studies reported treatment adherence assessed by two methods: self-reported adherence and/or pill count at the end of the study. The Rajasingham *et al* study additionally conducted remote blood sampling to verify HCQ concentrations in a subset. Adherence varied significantly across the studies, with a low proportion of approximately 52% in the Rojas-Serrano *et al* study and 97%–98% in the Abella *et al* study.

Results of meta-analysis

Overall, 3.4% (171 of 5039) developed PCR-confirmed SARS-CoV-2 infection and 5.6% (230 of 4087) developed suspected COVID-19 that was not laboratory confirmed. Since the goodness-of-fit assessment using Watanabe-Akaike information criterion concluded that the random-effects meta-analysis model was as good as or better than the fixed-effects meta-analysis model for all outcomes, we reported the results under the random-effects model. Compared with placebo, HCWs randomised to HCQ had numerically lower rate of PCR-confirmed SARS-CoV-2 infection cases (OR 0.92, 95% CI: 0.58, 1.37; GRADE score: moderate certainty), and suspected or probable SARS-CoV-2 infection cases (OR 0.78, 95% CI: 0.57, 1.10; GRADE score: moderate certainty). None of these ORs were statistically significant. Participants treated with HCQ had a numerically higher rate of adverse events (OR 1.35, 95% CI: 1.03, 1.73; GRADE score: moderate certainty) with statistical significance (figure 2). The outcome data used in our analyses are presented in online supplemental table 6. The summary of GRADE score assessment is provided in online supplemental table 7.

The Bayesian posterior probabilities of the OR less than 1 for the confirmed SARS-CoV-2 infection outcome (ie, the probability of HCQ favouring over placebo) was 0.67, while the posterior probability of OR less than 0.5 (ie, the probability that the odds of having a confirmed SARS-CoV-2 infection outcome in HCQ is less than a half of the odds in placebo) was 0.009. The posterior probability of the OR greater than 2 for the adverse event outcome (ie, the probability that the odds of having an adverse event in HCQ is greater than twice of the odds in placebo) was 0.004.

Our meta-analysis showed little or moderate variability of effect estimates across studies with I^2 value of 0%, 0% and 43%, and the estimated SD of the random effects of 0.39, 0.26 and 0.45 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection and adverse event outcomes, respectively. Funnel plots (online supplemental figure) showed no indication of publication bias and the associated Egger's test results supported that the funnel plots were not asymmetrical with p values of 0.308, 0.305 and 0.794 for the confirmed SARS-CoV-2 infection, suspected SARS-CoV-2 infection and adverse event outcomes, respectively.

DISCUSSION

Understanding the pre-exposure prophylactic effect of HCQ against COVID-19 remains relevant, as its use continues, particularly in the international setting.[28 29] Our meta-analysis of the 10 RCTs investigating the safety and efficacy of HCQ as PrEP in 5079 HCWs found that HCQ did not have a statistical association with fewer confirmed or suspected/probable SARS-CoV-2 infection cases compared with placebo. The geographical locations of the 10 trials included in the meta-analysis are the USA, Canada, Mexico, India, Spain, Bolivia, Venezuela, Peru and Pakistan (online supplemental table 3). While the ORs of most studies favour HCQ, the CIs remain wide suggesting low certainty in the true point estimate. Two studies including the Llanos-Cuentas *et al*[30] study conducted in Peru and the Syed *et al*[17] study conducted in Pakistan showed ORs favouring placebo, though the CIs remain wide. Furthermore, in this population, COVID-19 event rates were low, particularly for the most relevant PCR-confirmed infection outcome. The low event rate raises further concern for the uncertainty of these outcomes. Thus, if there is a minimal effect, the absolute benefit would be low. To gain more certainty, a very large study would need to be done and this is difficult to support now due to availability of highly effective vaccines. The safety profile of HCQ in the outpatient setting is well understood.[31] In these outpatient studies, there was statistically significant difference in adverse events in the HCQ versus the placebo arm, indicating that HCQ is less safe than placebo.

Our findings can be applied to HCWs but should not be generalised to a broader population. Our systematic search found only one published RCT of PrEP for non-HCW populations and the study was excluded from our meta-analysis. This study was conducted in Singapore[32] and showed a significant reduction in the risk of COVID-19 infection in the HCQ arm when compared with the comparator arm, vitamin C. However, this study showed moderate risk of bias as it used an open-label cluster randomisation design, the Institutional Review Board excluded higher risk persons from the HCQ arm only and the participants may not be representative of a general population due to the communal living environment.

A Bayesian meta-analysis approach was used to fit the data. The Bayesian meta-analysis approach has several advantages. First, its flexibility and the MCMC sampling methods to estimate posterior distributions provide probability-based quantities (eg, posterior probability of an OR smaller than 0.5) that complement typical meta-analysis results (eg, ORs and the associated CIs) and help decision-making.[33] Second, the Bayesian meta-analysis model with random effects estimates the between-study variability better than the frequentist counterparts.[34] Third, when it comes to binary outcomes, the Bayesian approach handles rare events better than the frequentist counterparts.[20]

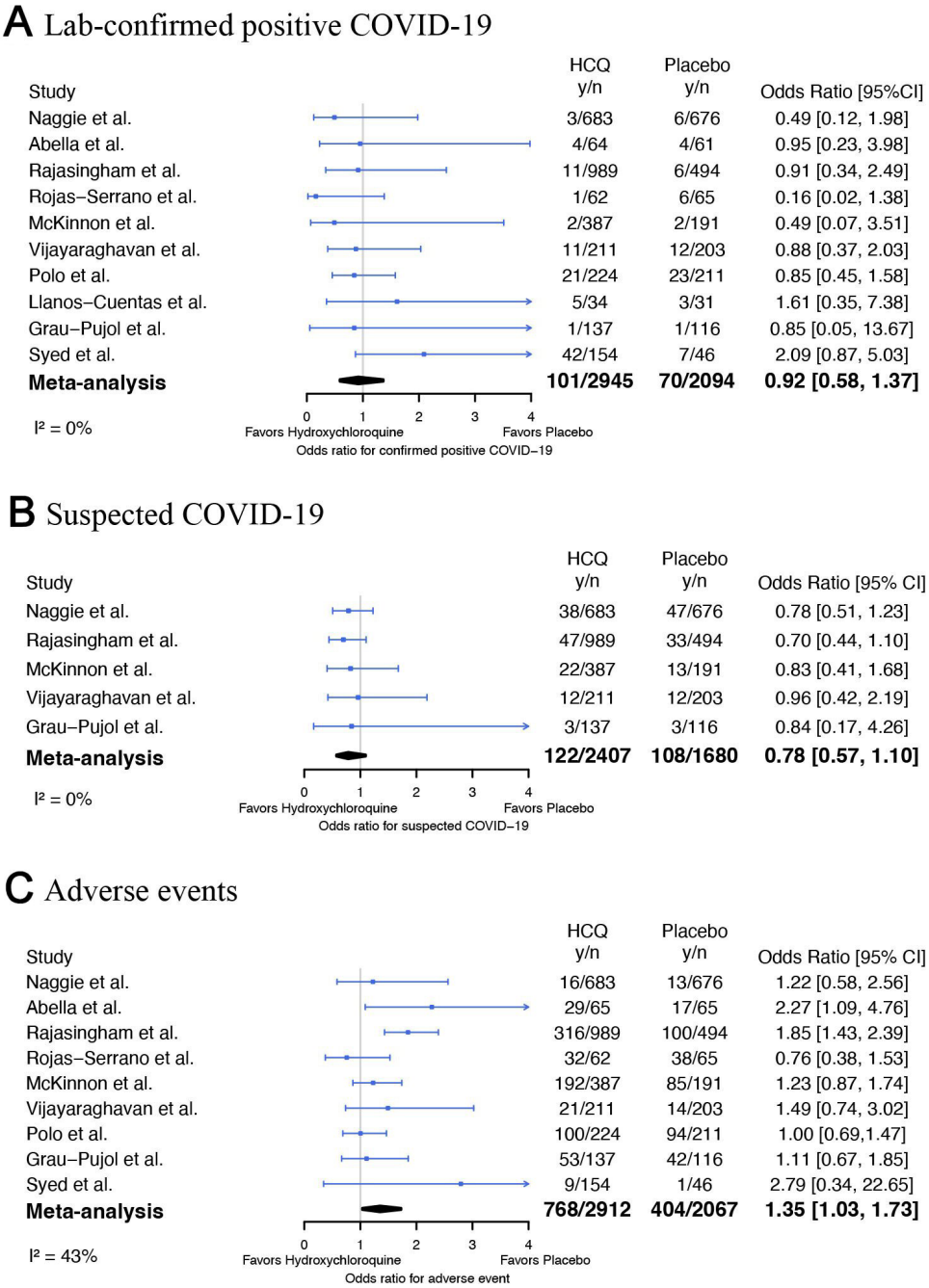

Figure 2 Forest plots of the meta-analysis results showing the number of events (y), sample size (n), posterior median of ORs and the associated 95% credible intervals (CIs) comparing HCQ versus placebo for (A) laboratory-confirmed positive COVID-19, (B) suspected COVID-19 and (C) adverse events. HCQ, hydroxychloroquine.

A recently published meta-analysis by García-Albéniz *et al*[35] investigated pre-exposure (seven RCTs included) and post-exposure (four RCTs included) prophylactic effects of HCQ, but not limited to the HCW population. They found significant pre-exposure prophylactic effects of HCQ on SARS-CoV-2 infection, different from ours. The seven PrEP RCTs included in the García-Albéniz *et al* meta-analysis consisted of six RCTs that were in our meta-analysis and the aforementioned Singapore study that was excluded from our meta-analysis. Our meta-analysis provides the most up-to-date, systematic and comprehensive evidence about prophylactic effects of HCQ focusing on the HCW population.

Although a meta-analysis allows for combining evidence from multiple studies in a principled way, our meta-analysis has limitations. First, our analysis did not evaluate effects of different HCQ doses and combined multiple HCQ arms using different doses in three studies. The RCTs included in our meta-analysis studied varying dosing schemes and a meta-analysis using aggregate-level data is not a sufficient source to study dosing effects. Second, detailed subgroup analyses were not conducted due to

limited information. Individual-level data are required to study both dosing and subgroup effects.

Our meta-analysis of 10 RCTs investigating safety and efficacy of HCQ as PrEP in HCWs provides the most up-to-date evidence on HCQ. Although most individual trials were underpowered and showed null data, integrating the results systematically via meta-analysis contributes to the scientific literature and provides certain answers to the question. We found that HCQ does not reduce the risk of confirmed or probable SARS-CoV-2 infection, but increase risk of adverse events compared with placebo. HCQ should not be used for PrEP in the HCW population.

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Contributors HH, SN, RR and KJA designed the study. HH is the guarantor. HH, AF and MH collected and analysed the data. HH, SN and RR wrote the manuscript. SH and KJA provided statistical review, while AF, JEM, RA, JR-S, BSA, AMP-V, CWW, AFH and DRB provided clinical review. All authors approved and decided to submit the paper for publication.

Funding This study is funded by the Patient Centered Outcomes Research Institute (PCORI; contract number COVID-19-2020-001).

Disclaimer The funder had no role in the design, conduct, analysis or reporting of this study.

Competing interests All authors except BSA reported no financial relationship with commercial interest. BSA has received NIH funds for COVID-19-related research and holds equity in VOC Health, a start-up company that is developing novel COVID-19 testing.

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 Ethics approval was not required because this study used publicly available aggregate data that were not involved with patients' information or prospective data collection.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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Supplementary Materials

CONTENTS

eTable 1. Search code that was used to identify publications as of March 14, 2023

PubMed search

#1	covid[Title] OR coronavirus[Title] OR sars-cov-2[Title]
#2	hydroxychloroquine[Title]
#3	randomized[Title/Abstract] OR randomized[Title/Abstract]
#4	#1 AND #2 AND #3

Embase search

#1	covid:ti OR coronavirus:ti OR 'sars cov 2':ti
#2	hydroxychloroquine:ti
#3	randomized:ab,ti OR randomised:ab,ti
#4	#1 AND #2 AND #3

eTable 2. Risk of bias for trials included in the meta-analysis using the Cochrane risk assessment tool. Green circle is for low risk and yellow circle is for some concerns

	Selection bias (Randomization process)	Performance bias (Deviations from the intended interventions)	Attrition bias[1] (Missing outcome data)	Reporting bias (Measurement of the outcome)	Other sources of bias (Selection of the reported result)
Naggie et al. (HERO-HCQ)					
Abella et al. (PATCH)					
Rajasingham et al. (MN-COVID-PREP)					
Rojas-Serrano et al.					
McKinnon et al. (WHIP)					
Vijayaraghavan et al.					
Polo et al. (EPICOS)					
Llanos-Cuentas et al.					
Grau-Pujol et al.					
Syed et al.					

[1] The Rojas-Serrano et al. study reported minimal loss to follow-up (<10%). The Rojas-Serrano et al. study reported 18% (25/130) lost to follow-up and additional 12% (16/130) discontinued the intervention.

eTable 3. Characteristics of trials included in the meta-analysis

	Naggie et al. (HERO-HCQ)	**Abella et al. (PATCH)**	**Rajasingham et al. (MN-COVID-PREP)**	**Rojas-Serrano et al.**	**McKinnon et al. (WHIP)**
N (randomization)	1360	132	1496	130	624
Study start date[1]	4/22/2020	4/9/2020	4/6/2020	4/21/2020	4/10/2020
Study completion date[2]	1/9/2021	11/13/2020	7/13/2020	3/31/2021	12/14/2020
Occupation	HCWs at risk of COVID exposure through work in the ICU, emergency department, emergency services, respiratory services or COVID unit	HCWs (Physicians, nurses, certified nursing assistants, emergency technicians, respiratory therapists) eligible working >20 hrs/week	HCWs (physicians, nurses, emergency medical technicians) with direct contact with COVID patients including emergency department and ICU setting, first responders and performing aerosol generating procedures	HCWs (nurses, nursing aids, cleaning staff, orderlies, respiratory therapists and physicians) taking care of hospitalized patients with COVID	HCW, first responders and correlational/law officers, nursing home workers, medical students, public transit workers, household family members of HCW in Michigan and Ohio
Sites	34 sites across the US	2 tertiary urban hospitals	Multiple sites nationwide across US and Canada	Single site (National Institute of Respiratory Diseases of Mexico)	Multiple sites at Michigan in the US
Randomization	Yes (Phase III)	Yes (Phase II)	Yes (Phase III)	Yes (Phase III)	Yes (Phase III)
Trial type	Double-blinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	No weight requirement	<40kg excluded	<50kg excluded	N/A
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Excluded	Excluded	Excluded	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Included	Exclude
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Included	
Significant renal disease (stage IV or greater)	Excluded	Included	Excluded	Excluded	Exclude
Pregnant/breastfeeding	Included	Excluded	Included in US, Excluded in Canada	Excluded	Exclude
Medication					
Qtc prolonging medications	Excluded	Excluded	Excluded	Included	Exclude
Use of other medications with significant drug interactions	Included	Excluded	Excluded	Included	N/A
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine or azithromycin)	Any treatment for COVID-19 within 14 days excluded	Current use of HCQ or chloroquine excluded	HCQ or chloroquine within 30 days excluded	Chronic use of HCQ included
COVID-19 related criteria					
Active or prior COVID	Excluded	N/A	Excluded	Excluded	Excluded
Fevers, cough, SOB	Excluded	Excluded if symptoms within 2 weeks unless negative COVID test	Excluded	Excluded	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	N/A
Positive COVID serology	Included	Included	N/A	Included	N/A
Analysis	Modified intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat

	Vijayaraghavan et al.	Polo et al. (EPICOS)	Llanos-Cuentas et al.	Grau-Pujol et al.	Syed et al.
N (randomization)	416	454	68	269	200
Study start date[1]	6/29/2020	4/2020 Spain, 10/2020 Bolivia, 3/2021 Venezuela	June, 2020	4/4/2020	5/1/2020
Study completion date[2]	2/4/2021	5/30/2021	November, 2020	Study halted a 1 month analysis	Not reported
Occupation	HCWs in an environment with exposure to COVID-19 (physicians, nurses, allied health workers and ancillary health workers)	HCWs (physicians, nurses, medical students, other workers with and without direct patient contact)	HCWs (physicians, nursing staff, technical staff and nursing assistants involved in care of COVID-19 patients)	HCWs (physicians, nurses, nurse assistants and administrators working at least 3 days a week in the trial hospitals)	HCWs at risk of COVID-19 exposure including physicians, nurses, first responders, those performing aerosol generating procedures or working in the emergency department, ICU, and general medicine wards
Sites	9 hospitals across India	Multiple sites across Spain, Venezuela and Bolivia	4 public hospitals across the Lima metropolitan area	3 hospitals in Barcelona, Spain	Single hospital in Pakistan
Randomization	Yes	Yes	Yes (Phase III)	Yes	Yes (Phase II)
Trial type	Unblinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
	Eligibility criteria				
Age	>18	>18-70	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	<40kg excluded	No weight requirement	No weight requirement	<40 kg
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Included	Excluded	Included	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Excluded	Excluded
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Excluded	Excluded
Significant renal disease (stage IV or greater)	Included	Excluded	Excluded	Excluded	Excluded
Pregnant/breastfeeding	Excluded	Excluded	Included	Excluded	Excluded
Medication					
Qtc prolonging medications	Excluded	Excluded	Included	Excluded	Excluded
Use of other medications with significant drug interactions	Excluded	Included	Included	Excluded	Excluded
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine azithromycin)	Any medication as prophylaxis against COVID-19 after 3/1/21	Use of hydroxychloroquine, chloroquine or azithromycin in the last 30 days excluded	Treatment with chloroquine or hydroxychloroquine within the last 1 month	Those already taking hydroxychloroquine were excluded
COVID-19 related criteria					
Active or prior COVID	Excluded	Excluded	Excluded	Excluded	Excluded
Fevers, cough, SOB	Not specified in exclusion criteria	Excluded	Not specified in exclusion criteria	Not specified in exclusion criteria	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	Excluded
Positive COVID serology	N/A	N/A	N/A	Excluded	Excluded
Analysis	Intention-to-treat	Not reported	Intention-to-treat	Intention-to-treat	Not reported

HCW=Healthcare workers; ICU=Intensive care unit; [1] Date when first participant was enrolled; [2] Date when final data were collected for the last participant

eTable 4. Definition of adverse events

Trial	AE definition
Naggie et al. (**HERO-HCQ**)	Adverse events include general disorders and administration site conditions, psychiatric disorders, skin and subcutaneous tissue disorders, cardiac disorders, infections and infestations, nervous system disorders, gastrointestinal disorders, investigations (electrocardiogram QT prolonged and heart rate increased), ear and labyrinth disorders, renal and urinary disorders, and respiratory, thoracic and mediastinal disorders.
Abella et al. (**PATCH**)	Adverse events include abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness.
Rajasingham et al. (**MN-COVID-PREP**)	Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and others.
Rojas-Serrano et al.	Examples of adverse events are as follows: abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness. Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and other.
McKinnon et al. (**WHIP**)	Covid-19 related symptoms, covid-19 clinical disease and medication adverse effects including gastrointestinal disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, cardiac disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, skin and subcutaneous tissue disorders, ear and labyrinth disorders, and eye disorders.
Vijayaraghavan et al.	Adverse events listed in each category at the participant level were categorized as cardiac, gastro-intestinal, headache, and Qtc prolongation.
Polo et al. (EPICOS)	Adverse events were classified by organ system and included: gastrointestinal disorders, blood and lymphatic system disorders, cardiac disorders, ear and labyrinth disorders, eye disorder, general disorders, immune system disorder, infections, injuries, investigations, metabolism and nutrition disorders, musculoskeletal/connective tissue disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system disorders, respiratory disorders, skin disorders and vascular disorders.
Llanos-Cuentas et al.	Adverse events from grade 1 to grade 3 and above. Note that the Llanos-Cuentas et al. study did report the number of adverse events (not participants) in the HCQ group only. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.
Grau-Pujol et al.	Adverse events included: general symptoms (fever, chills, sweating, malaise, myalgia, arthralgia), gastrointestinal symptoms (nausea, abdominal pain, diarrhea, dysgeusia), dermatological symptoms (itching, rash),respiratory symptoms (rhinorrhea, sore throat / odynophagia, cough, pleuritic pain, dyspnea), neurologic symptoms (headache, visual disturbances), and cardiovascular symptoms. Events were graded mild, moderate and severe.
Syed et al.	Syed et al. report the number of patients in each group who experienced adverse events, but did not report what the events were. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.

eTable 5. Baseline characteristics with additional variables and detailed information. Sample mean and standard deviation (in parenthesis) are reported for continuous variables, and the number of participants and proportion (in parenthesis) are reported for binary or categorical variables.

		Naggie et al. (HERO-HCQ)		**Abella et al. (PATCH)**		**Rajasingham et al. (MN-COVID-PREP)**		**Rojas-Serrano et al.**		**McKinnon et al. (WHIP)**	
		HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	683	676	66	66	989	494	62	65	387	191
	Age	44.2 (11.9)	43.1 (11.2)	31 (20-66)[3]	34 (23-62)[3]	41.5 (35, 49)[3]	40 (34, 48)[3]	31.0 (26.4-39)[4]	31.9 (27.2-43.7)[4]	45.7 (11.6); 44.9 (11.4)[2]	44.1 (12.7)
	Female	442 (64.7%)	446 (66.0%)	54 (82%)	37 (56%)	519 (52.5%)	241 (48.8%)	29 (42.6%)	42 (64.6%)	220 (57%)	114 (60%)
	BMI (kg/m^2)	28.3 (6.3)	28.6 (6.7)	26 (19-37)[5]	26 (20-50)[5]			26.7 (3.9)	27.2 (4.6)		
	Current smoker			0 (0%)	0 (0%)	38 (3.84%)	13 (2.6%)	20 (32.2%)[6]	23 (35.4%)[6]		
Race/ Ethnicity	White	624 (91.4%)	610 (90.2%)	55 (83%)	54 (82%)	852 (86.1%)	419 (84.8%)			334 (86%)	161 (84%)
	Asian			7 (11%)	7 (11%)	46 (4.7%)	29 (5.9%)			23 (6%)	15 (8%)
	African American	18 (2.6%)	23 (3.4%)	3 (4%)	1 (2%)	10 (1.0%)	10 (2.0%)			15 (4%)	9 (5%)
	Hispanic	39 (5.7%)	40 (5.9%)	0 (0%)	2 (3%)	40 (4.0%)	18 (3.6%)			11 (3%)	7 (4%)
Comorbidities	Asthma	58 (8.5%)	77 (11.4%)	9 (14%)	14 (21%)	91 (9.2%)	59 (11.9%)				
	Diabetes	20 (2.9%)	35 (5.2%)	1 (2%)	3 (5%)	36 (3.6%)	14 (2.8%)				
	Hypertension	99 (14.5%)	99 (14.6%)	3 (5%)	14 (21%)	145 (14.7%)	60 (12.1%)				
	None			54 (82%)	40 (61%)	646 (65.3%)	336 (68.0%)	53 (85.5%)	58 (89.2%)		
Practice Location	Emergency Department	96 (14.1%)	94 (13.9%)	38 (58%)	36 (55%)	417 (42.2%)	190 (38.5%)			48 (12%)	19 (10%)
	Internal Medicine ward			17 (26%)	18 (27%)	98 (9.9%)	56 (11.3%)			31 (8%)	20 (10%)
	ICU/anesthesia			6 (9%)	6 (9%)						
	Labor and delivery			5 (7%)	6 (9%)						
	Ambulance	66 (9.7%)	63 (9.3%)			73 (7.4%)	45 (9.1%)				
	Congregate care setting					46 (4.7%)	20 (4.0%)				
	ICU	48 (7.0%)	59 (8.7%)			184 (18.6%)	85 (17.2%)			37 (10%)	23 (12%)
	Operating room					103 (10.4%)	75 (15.2%)				
	EMS, Fire and Police First Responders									32 (8%)	16 (8%)
Occupation	Nurse	186/677 (27.5%)	167/668 (25.0%)	46 (70%)	42 (64%)						
	Physician	143/677 (21.1%)	144/668 (21.6%)	11 (17%)	16 (24%)						
	Certified Nurse Assistant			2 (3%)	2 (3%)						
	ED Technician			3 (4%)	1 (2%)						
	Respiratory therapist	15/677 (2.2%)	18/668 (2.7%)	3 (4%)	5 (7%)						
	Nurse or Physician							31 (50%)	33 (50.8%)		
	Emergency Medicine Provider					407 (41.1%)	190 (38.5%)				
	ICU provider					160 (16.2%)	83 (16.8%)				
	Anesthesia/ENT					178 (18.0%)	105 (21.3%)				
	HCW in COVID unit					76 (7.7%)	29 (5.9%)				
	Healthcare worker in congregate care setting					11 (1.1%)	4 (0.8%)				
	First responder					115 (11.6%)	65 (13.2%)				

		Vijayaraghavan et al.		Polo et al. (EPICOS)		Llanos-Cuentas et al.		Grau-Pujol et al.		Syed et al.	
		HCQ	Placebo	HCQ[2]	Placebo	HCQ	Placebo	HCQ	Placebo	HCQ[1]	Placebo
	N (randomization)	213	203	231	223	36	32	142	127	154	46
	Age	32.3 (9.65)	31.8 (8.63)	38 (18-65)	38 (18,65)	39.14 (1.53)	39.28 (1.72)	39.6 (11.2)	40.3 (12.8)	30.25 (NA)	31.9 (9.13)
	Female	100 (46.9%)	97 (47.8%)	149 (64.5%)	143 (64.1%)	20 (55.6%)	20 (62.5%)	104 (73.2%)	93 (73.2%)	68 (44.1%)	23 (50%)
	BMI (kg/m^2)										
	Current smoker	8 (3.8%)	9 (4.4%)					21 (14.9%)	17 (13.8%)	19 (12.3%)	7 (15.2%)
Race/ Ethnicity	White										
	Asian										
	African American										
	Hispanic										
Comorbidities	Asthma	0 (0%)	0 (0%)	20 (8.7%)	9 (4.0%)	3 (8.3%)	4 (12.5%)	5 (3.5%)	2 (1.6%)		
	Diabetes	7 (3.3%)	3 (1.5%)	1 (0.4%)	3 (1.3%)	1 (2.8%)	0 (0%)	0 (0%)	1 (0.8%)	4 (2.6%)	3 (6.5%)
	Hypertension	2 (0.9%)	3 (1.5%)	4 (1.7%)	19 (8.5%)	3 (8.3%)	2 (6.3%)	2 (1.4%)	3 (2.4%)	7 (4.5%)	2 (4.3%)
	None										
Practice Location	Emergency Department	26 (12.2%)	18 (8.9%)	20 (8.7%)	21 (9.4%)						
	Internal Medicine ward	130 (64%)	130 (61%)								
	ICU/anesthesia										
	Labor and delivery										
	Ambulance			0 (0%)	0 (0%)						
	Congregate care setting										
	ICU	53 (24.9%)	53 (26.1%)	17 (7.4%)	13 (5.8%)						
	Operating room										
	EMS, Fire and Police First Responders										
Occupation	Nurse	67 (31.5%)	68 (33.5%)	67 (29.0%)	72 (32.3%)	6 (16.7%)	5 (15.6%)	35 (27.8%)	40 (28.2%)	20 (13.0%)	9 (19.6%)
	Physician	34 (16%)	31 (15.3%)	74 (32%)	66 (29.6%)	23 (63.9%)	16 (50%)	67 (47.2%)	53 (42.1%)	118 (76.6%)	25 (54.3%)
	Certified Nurse Assistant					1 (2.8%)	0 (0%)	12 (8.5%)	12 (9.5%)		
	ED Technician										
	Respiratory therapist										
	Nurse or Physician										
	Emergency Medicine Provider									2 (1.3%)	0 (0%)
	ICU provider										
	Anesthesia/ENT										
	HCW in COVID unit										
	Healthcare worker in congregate care setting										
	First responder									2 (1.3%)	0 (0%)

HCQ=Hydroxychloroquine ; ITT= Intention-to-treat ; BMI=Body mass index ; ICU=Intensive care unit; ED=Emergency department ; ENT=Ear, nose, throat ; HCW=Healthcare worker

[1] More than one HCQ groups with different doses are lumped.

[2] The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

[3] Median (range)

[4] Median (IQR)

[5] Mean (range)

[6] Current or previous smoker

eTable 6. Results of outcome measures in trials included in the meta-analysis. Sample size and the number of participants who had each outcome are reported with proportions (%) in parentheses.

	Treatment	N (ITT)	Confirmed COVID-19	Suspected with COVID compatible symptoms	Adverse event[2]
Naggie et al. (HERO-HCQ)	HCQ	683	3 (0.4)	38 (5.6)	16 (2.3)
	Placebo	676	6 (0.9)	47 (7.0)	13 (1.9)
Abella et al. (PATCH)	HCQ	64	4 (6.3)		29 (45.3)
	Placebo	61	4 (6.6)		17 (27.9)
Rajasingham et al. (MN-COVID-PREP)	HCQ[1]	989	11 (1.1)	47 (4.8)	316 (32.0)
	Placebo	494	6 (1.2)	33 (6.7)	100 (20.2)
Rojas-Serrano et al.	HCQ	62	1 (1.6)		32 (51.6)
	Placebo	65	6 (9.2)		38 (58.5)
McKinnon et al. (WHIP)	HCQ[1]	387	2 (0.5)	22 (5.7)	192 (49.6)
	Placebo	191	2 (1.0)	13 (6.8)	85 (44.5)
Vijayaraghavan et al.	HCQ	211	11 (5.2)	12 (5.7)	21 (10.0)
	Placebo	203	12 (5.9)	12 (5.9)	14 (6.9)
Polo et al. (EPICOS)	HCQ	224	21 (9.4)		100 (44.6)
	Placebo	211	23 (10.9)		94 (44.5)
Llanos-Cuentas et al.	HCQ	34	5 (14.7)		
	Placebo	31	3 (9.7)		
Grau-Pujol et al.	HCQ	137	1 (0.7)	3 (2.2)	53 (38.7)
	Placebo	116	1 (0.9)	3 (2.6)	42 (36.2)
Syed et al.	HCQ[1]	154	42 (27.3)		9 (5.8)
	Placebo	46	7 (15.2)		1 (2.2)

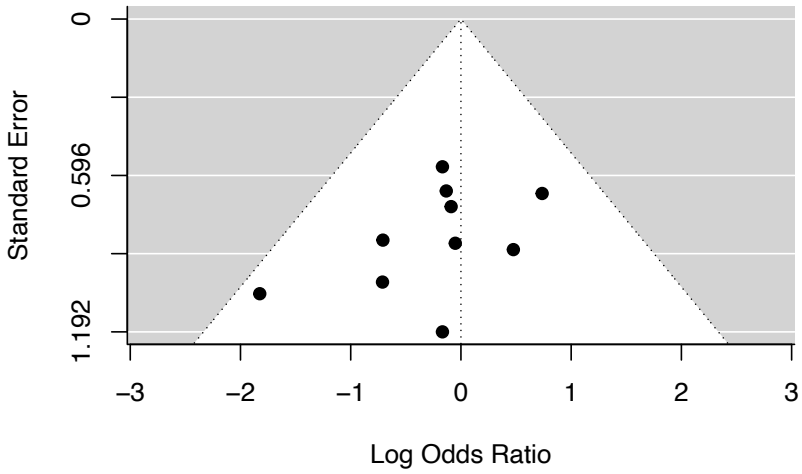
HCQ= Hydroxychloroquine; ITT= Intention-to-treat; AE=Adverse event ; COVID-RS=COVID-19 related symptoms ; Vit C= Vitamin C

[1] More than one HCQ groups with different doses are lumped.

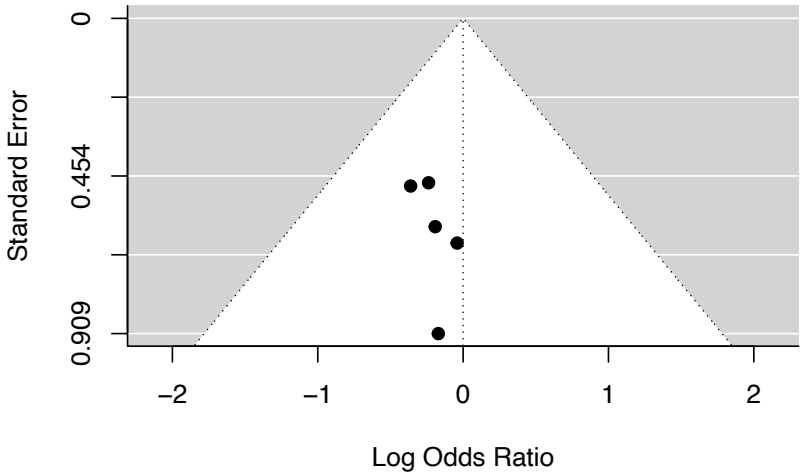
[2] Number of patients with any adverse events

eFigure. Funnel plots for the three outcomes

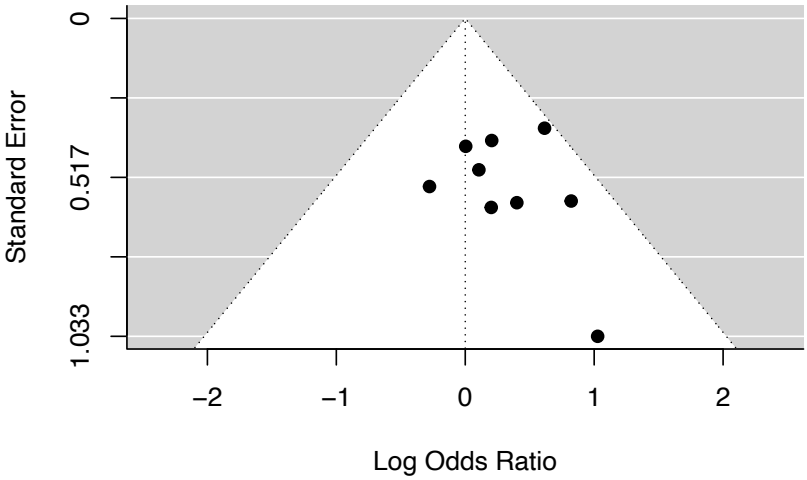
(a) Lab-confirmed positive COVID-19



(b) Suspected COVID-19



(c) Adverse events



eTable 7. GRADE summary of findings table

Outcomes	**No of participants (studies) Follow up**	**Quality of the evidence (GRADE)**	**Odds ratio (95% Confidence Interval)**
Lab-confirmed positive COVID-19	5039 (10 studies) From 28 days to 180 days	⨁⨁⨁⨀ **Moderate**[1] due to imprecision	0.92 (0.58, 1.37)
Suspected COVID-19	4087 (5 studies) From 56 days to 180 days	⨁⨁⨁⨀ **Moderate**[1] due to imprecision	0.78 (0.57, 1.10)
Adverse events	4979 (9 studies) From 56 days to 180 days	⨁⨁⨁⨀ **Moderate**[2] due to imprecision	1.35 (1.03, 1.73)

[1]95% confidence interval includes effect suggesting benefit as well as no benefit.
[2]Although the 95% confidence interval includes an effect suggesting no benefit, we decided to downgrade it by one level because the lower limit is close to the null.

GRADE Working Group grades of evidence is available here:
https://gdt.gradepro.org/app/handbook/handbook.html