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

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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.

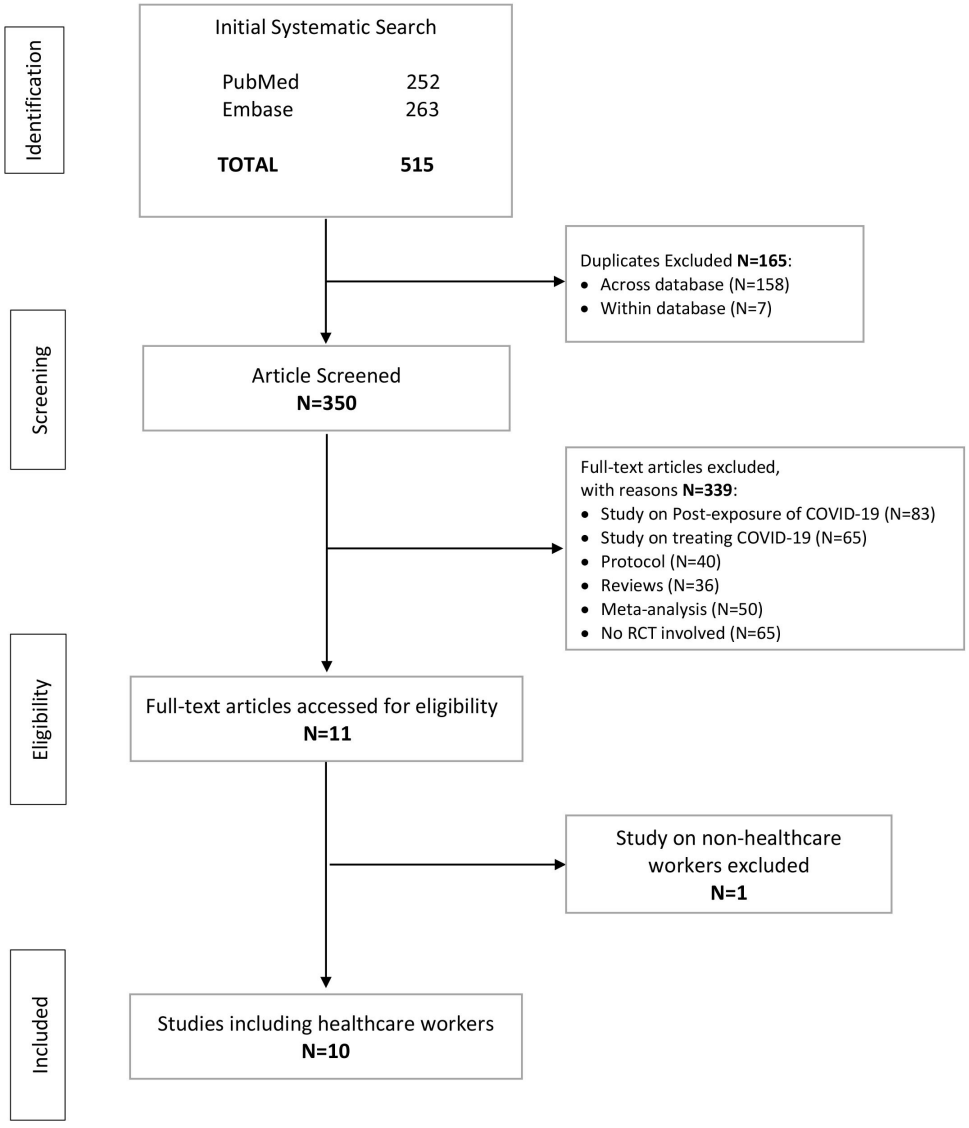

Figure 1 Flow chart of literature review. RCT, randomised controlled trial.

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]

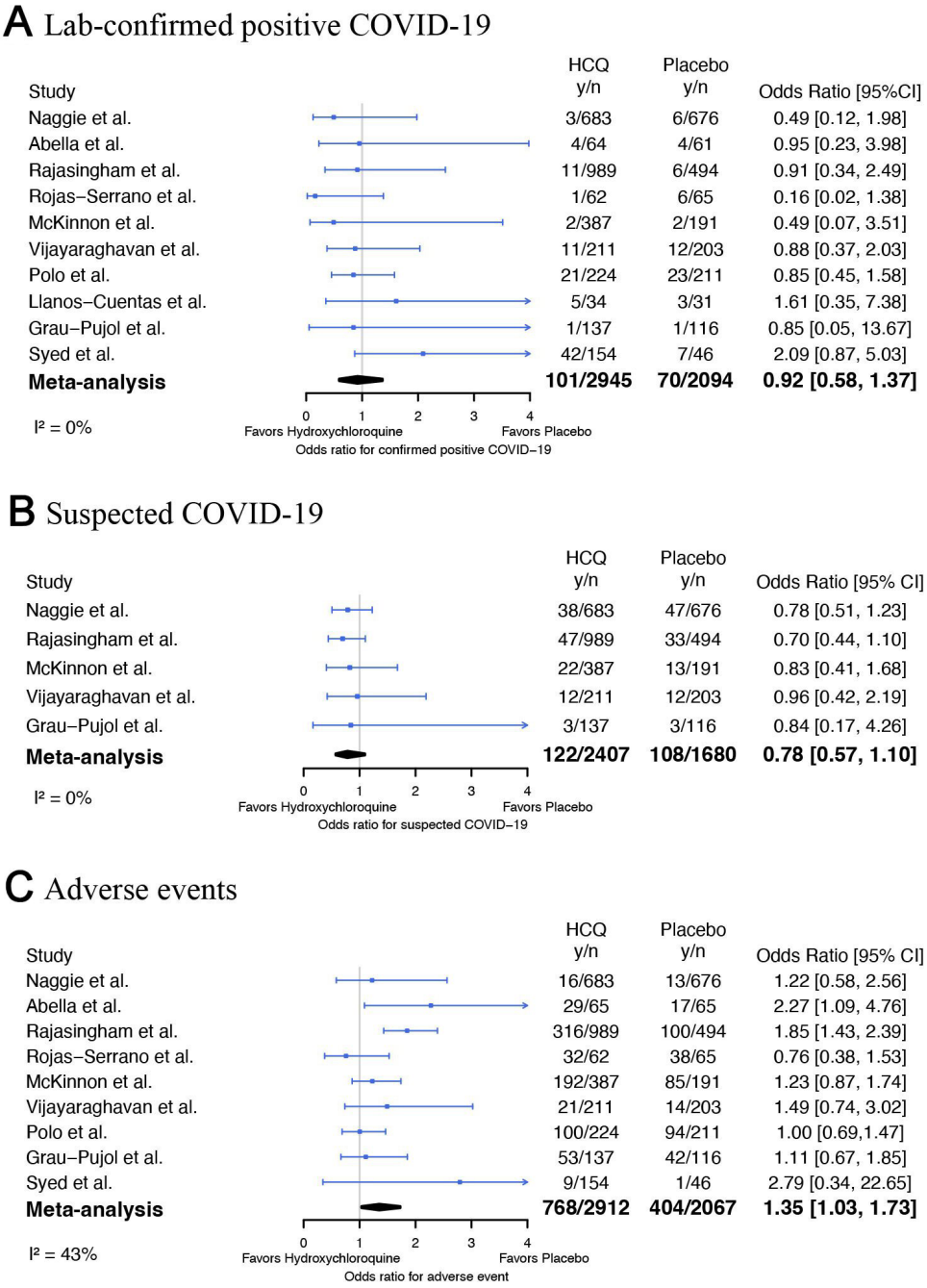

Figure 2 Forest plots of the meta-analysis results showing the number of events (y), sample size (n), posterior median of ORs and the associated 95% credible intervals (CIs) comparing HCQ versus placebo for (A) laboratory-confirmed positive COVID-19, (B) suspected COVID-19 and (C) adverse events. HCQ,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

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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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