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Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19 (Review)

Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T

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[Intervention Review]

Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19

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ABSTRACT

Background

The coronavirus disease 2019 (COVID-19) pandemic has resulted in substantial mortality. Some specialists proposed chloroquine (CQ) and hydroxychloroquine (HCQ) for treating or preventing the disease. The efficacy and safety of these drugs have been assessed in randomized controlled trials.

Objectives

To evaluate the effects of chloroquine (CQ) or hydroxychloroquine (HCQ) for

1) treating people with COVID-19 on death and time to clearance of the virus;

2) preventing infection in people at risk of SARS-CoV-2 exposure;

3) preventing infection in people exposed to SARS-CoV-2.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Current Controlled Trials (www.controlled-trials.com), and the COVID-19-specific resources www.covid-nma.com and covid-19.cochrane.org, for studies of any publication status and in any language. We performed all searches up to 15 September 2020. We contacted researchers to identify unpublished and ongoing studies.

Selection criteria

We included randomized controlled trials (RCTs) testing chloroquine or hydroxychloroquine in people with COVID-19, people at risk of COVID-19 exposure, and people exposed to COVID-19.

Adverse events (any, serious, and QT-interval prolongation on electrocardiogram) were also extracted.

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Data collection and analysis

Two review authors independently assessed eligibility of search results, extracted data from the included studies, and assessed risk of bias using the Cochrane 'Risk of bias' tool. We contacted study authors for clarification and additional data for some studies. We used risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, with 95% confidence intervals (CIs). We performed meta-analysis using a random-effects model for outcomes where pooling of effect estimates was appropriate.

Main results

1. Treatment of COVID-19 disease

We included 12 trials involving 8569 participants, all of whom were adults. Studies were from China (4); Brazil, Egypt, Iran, Spain, Taiwan, the UK, and North America (each 1 study); and a global study in 30 countries (1 study). Nine were in hospitalized patients, and three from ambulatory care. Disease severity, prevalence of comorbidities, and use of co-interventions varied substantially between trials. We found potential risks of bias across all domains for several trials.

Nine trials compared HCQ with standard care (7779 participants), and one compared HCQ with placebo (491 participants); dosing schedules varied. HCQ makes little or no difference to death due to any cause (RR 1.09, 95% CI 0.99 to 1.19; 8208 participants; 9 trials; high-certainty evidence). A sensitivity analysis using modified intention-to-treat results from three trials did not influence the pooled effect estimate.

HCQ may make little or no difference to the proportion of people having negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment (RR 1.00, 95% CI 0.91 to 1.10; 213 participants; 3 trials; low-certainty evidence). HCQ probably results in little to no difference in progression to mechanical ventilation (RR 1.11, 95% CI 0.91 to 1.37; 4521 participants; 3 trials; moderate-certainty evidence). HCQ probably results in an almost three-fold increased risk of adverse events (RR 2.90, 95% CI 1.49 to 5.64; 1394 participants; 6 trials; moderate-certainty evidence), but may make little or no difference to the risk of serious adverse events (RR 0.82, 95% CI 0.37 to 1.79; 1004 participants; 6 trials; low-certainty evidence). We are very uncertain about the effect of HCQ on time to clinical improvement or risk of prolongation of QT-interval on electrocardiogram (very low-certainty evidence).

One trial (22 participants) randomized patients to CQ versus lopinavir/ritonavir, a drug with unknown efficacy against SARS-CoV-2, and did not report any difference for clinical recovery or adverse events.

One trial compared HCQ combined with azithromycin against standard care (444 participants). This trial did not detect a difference in death, requirement for mechanical ventilation, length of hospital admission, or serious adverse events. A higher risk of adverse events was reported in the HCQ-and-azithromycin arm; this included QT-interval prolongation, when measured.

One trial compared HCQ with febuxostat, another drug with unknown efficacy against SARS-CoV-2 (60 participants). There was no difference detected in risk of hospitalization or change in computed tomography (CT) scan appearance of the lungs; no deaths were reported.

2. Preventing COVID-19 disease in people at risk of exposure to SARS-CoV-2

Ongoing trials are yet to report results for this objective.

3. Preventing COVID-19 disease in people who have been exposed to SARS-CoV-2

One trial (821 participants) compared HCQ with placebo as a prophylactic agent in the USA (around 90% of participants) and Canada. Asymptomatic adults (66% healthcare workers; mean age 40 years; 73% without comorbidity) with a history of exposure to people with confirmed COVID-19 were recruited. We are very uncertain about the effect of HCQ on the primary outcomes, for which few events were reported: 20/821 (2.4%) developed confirmed COVID-19 at 14 days from enrolment, and 2/821 (0.2%) were hospitalized due to COVID-19 (very low-certainty evidence). HCQ probably increases the risk of adverse events compared with placebo (RR 2.39, 95% CI 1.83 to 3.11; 700 participants; 1 trial; moderate-certainty evidence). HCQ may result in little or no difference in serious adverse events (no RR: no participants experienced serious adverse events; low-certainty evidence).

One cluster-randomized trial (2525 participants) compared HCQ with standard care for the prevention of COVID-19 in people with a history of exposure to SARS-CoV-2 in Spain. Most participants were working or residing in nursing homes; mean age was 49 years. There was no difference in the risk of symptomatic confirmed COVID-19 or production of antibodies to SARS-CoV-2 between the two study arms.

Authors' conclusions

HCQ for people infected with COVID-19 has little or no effect on the risk of death and probably no effect on progression to mechanical ventilation. Adverse events are tripled compared to placebo, but very few serious adverse events were found. No further trials of hydroxychloroquine or chloroquine for treatment should be carried out.

These results make it less likely that the drug is effective in protecting people from infection, although this is not excluded entirely. It is probably sensible to complete trials examining prevention of infection, and ensure these are carried out to a high standard to provide unambiguous results.

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PLAIN LANGUAGE SUMMARY

Is chloroquine or hydroxychloroquine useful in treating people with COVID-19, or in preventing infection in people who have been exposed to the virus?

What is the aim of this review?

COVID-19 is an infectious respiratory disease caused by a coronavirus called SARS-CoV-2. If the infection becomes severe, people may need intensive care and support in hospital, including mechanical ventilation.

Drugs used for other diseases were tried out in COVID-19, and this included chloroquine, used for malaria; and hydroxychloroquine used for rheumatic diseases, such as rheumatoid arthritis or systemic lupus erythematosus. We sought evidence of the effects of these drugs in treating people ill with the disease; in preventing the disease in people at risk of getting the disease, such as health workers; and people exposed to the virus developing the disease.

Key messages

Hydroxychloroquine does not reduce deaths from COVID-19, and probably does not reduce the number of people needing mechanical ventilation.

Hydroxychloroquine caused more unwanted effects than a placebo treatment, though it did not appear to increase the number of serious unwanted effects.

We do not think new studies of hydroxychloroquine should be started for treatment of COVID-19.

What was studied in the review?

We searched for studies that looked at giving chloroquine and hydroxychloroquine to people with COVID-19; people at risk of being exposed to the virus; and people who have been exposed to the virus.

We found 14 relevant studies: 12 studies of chloroquine or hydroxychloroquine used to treat COVID-19 in 8569 adults; two studies of hydroxychloroquine to stop COVID-19 in 3346 adults who had been exposed to the virus but had no symptoms of infection. We did not find any completed studies of these medicines to stop COVID-19 in people who were at risk of exposure to the virus; studies are still under way.

The studies took place in China, Brazil, Egypt, Iran, Taiwan, North America, and Europe; one study was worldwide. Some studies were partly funded by pharmaceutical companies that manufacture hydroxychloroquine.

What are the main results of our review?

Treating COVID-19

Compared with usual care or placebo, hydroxychloroquine:

· clearly did not affect how many people died (of any cause; 9 studies in 8208 people);

· probably did not affect how many people needed mechanical ventilation (3 studies; 4521 people);

· may not affect how many people still tested positive for the virus after 14 days (3 studies; 213 people).

We are uncertain whether hydroxychloroquine affected the number of people whose symptoms improved after 28 days.

Compared with other antiviral treatment (lopinavir plus ritonavir), chloroquine made little or no difference to the time taken for symptoms to improve (1 study; 22 people).

Compared with usual care in one study in 444 people, hydroxychloroquine given with azithromycin (an antibiotic) made no difference to:

· how many people died;

· how many needed mechanical ventilation; or

· time spent in hospital.

Compared with febuxostat (a medicine to treat gout), hydroxychloroquine made no difference to how many people were admitted to hospital or to changes seen on scans of people's lungs; no deaths were reported (1 study; 60 people).

Preventing COVID-19 in people exposed to it

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We are uncertain whether hydroxychloroquine affected how many people developed COVID-19, or how many people were admitted to hospital with COVID-19, compared with those receiving a placebo treatment (1 study; 821 people).

Compared with usual care, hydroxychloroquine made no difference to the risk of developing COVID-19, or antibodies to the virus, in people exposed to it (1 study; 2525 people).

Unwanted effects

When used for treating COVID-19, compared with usual care or placebo, hydroxychloroquine:

· probably increases the risk of mild unwanted effects (6 studies; 1394 people);

· may not increase the risk of serious harmful effects (6 studies; 1004 people).

When given along with azithromycin, hydroxychloroquine increased the risk of any unwanted effects, but made no difference to the risk of serious unwanted effects (1 study; 444 people).

Compared with lopinavir plus ritonavir, chloroquine made little or no difference to the risk of unwanted effects (1 study; 22 people).

When used for preventing COVID-19, hydroxychloroquine probably causes more unwanted effects than placebo, but may not increase the risk of serious, harmful unwanted effects (1 study; 700 people).

How confident are we in our results?

We are confident about our results for how many people died and moderately confident about how many needed mechanical ventilation. We are moderately confident about the unwanted effects of hydroxychloroquine treatment, but less confident about our results for serious unwanted effects; these results might change with further evidence.

How up-to-date is this review?

We included evidence published up to 15 September 2020.

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SUMMARY OF FINDINGS

Summary of findings 1. Hydroxychloroquine (HCQ) compared to standard care or placebo for the treatment of people with COVID-19

Patients or population: adults with mild to severe COVID-19

Settings: hospital inpatients and ambulatory care in the community

Intervention: HCQ

Comparison: standard care or placebo (no HCQ)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care or placebo	Risk with HCQ				
Death due to any cause	18 per 100	**19 per 100** (18 to 21)	**RR 1.09** (0.99 to 1.19)	8208 (9 RCTs)[a]	⊕⊕⊕⊕ HIGH [b,c]	HCQ results in little or no difference to death due to any cause.
Negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment[d]	83 per 100	**83 per 100** (76 to 91)	**RR 1.00** (0.91 to 1.10)	213 (3 RCTs)[e]	⊕⊕◯◯ LOW [f,g]	HCQ may make little or no difference to proportion of people having negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment.
Progression to mechanical ventilation	8 per 100	**9 per 100** (7 to 11)	**RR 1.11** (0.91 to 1.37)	4521 (3 RCTs)[h]	⊕⊕⊕◯ MODERATE [i,j]	HCQ probably results in little to no difference in progression to mechanical ventilation.
Time to clinical improvement	28 per 100	**28 per 100** (18 to 44)	**HR 1.01** (0.59 to 1.74)	119 (1 RCT)[k]	⊕◯◯◯ VERY LOW [f,l,m]	We are uncertain whether HCQ increases or decreases the proportion of people with clinical improvement at day 28 from enrolment.
Participants with any adverse events	16 per 100	**46 per 100** (24 to 90)	**RR 2.90** (1.49 to 5.64)	1394 (6 RCTs)[n]	⊕⊕⊕◯ MODERATE [o,p]	HCQ probably increases the risk of developing adverse events.
Participants with serious adverse events	36 per 1000	**30 per 1000** (13 to 64)	**RR 0.82** (0.37 to 1.79)	1004 (6 RCTs)[q]	⊕⊕◯◯ LOW [r]	HCQ may result in little or no difference to risk of serious adverse events.
Participants with prolongation of QT-interval on ECG	2 per 100	**17 per 100** (2 to 100)	**RR 8.47** (1.14 to 63.03)	147 (1 RCT)[s]	⊕◯◯◯ VERY LOW [t,u,v]	The evidence is very uncertain about the effect of HCQ on prolongation of QT-interval on ECG.

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*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **ECG:** electrocardiogram; **HCQ:** hydroxychloroquine; **HR:** hazard ratio; **PCR:** polymerase chain reaction **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020c; Horby 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020. Of these, no participants died in Chen 2020a; Chen 2020c; Mitjà 2020a; Tang 2020.

[b] Not downgraded for risk of bias, as most of the evidence comes from Horby 2020 and Pan 2020, which have low risk of bias for this outcome.

[c] Not downgraded for indirectness, but it is noted that the population in the largest trial, Horby 2020, was mostly severely/critically unwell.

[d] This was selected as the most relevant of three related outcomes reported by trials in this review. Analyses for the other outcomes (time to negative PCR for SARS-CoV-2 on respiratory samples; negative PCR for SARS-CoV-2 at day 7 from enrolment) did not demonstrate an important benefit/harm.

[e] Chen 2020a; Chen 2020c; Tang 2020.

[f] Downgraded by one level for serious indirectness: almost all people had mild or moderate COVID-19; all were hospitalized; and all were from one region.

[g] Not downgraded for imprecision: narrow confidence interval, not including appreciable benefit nor harm. The sample size has approximately 80% power to detect an absolute difference of 13%, or 90% power to detect an absolute difference of 15%, in this outcome for the group receiving HCQ versus those receiving standard care.

[h] Cavalcanti 2020; Horby 2020; Tang 2020.

[i] Not downgraded for indirectness: the three trials all recruited participants admitted to hospital.

[j] Downgraded by one level for serious imprecision: lower confidence interval bound represents no benefit nor harm from HCQ, whereas the upper bound suggests appreciable harm.

[k] Tang 2020.

[l] Downgraded by one level for serious risk of bias: unclear risk of attrition and reporting bias, and high risk of other bias.

[m] Downgraded by one level for serious imprecision: lower confidence interval bound represents appreciable harm from HCQ, whereas the upper bound suggests no appreciable benefit.

[n] Cavalcanti 2020; Chen 2020a; Chen 2020b; Mitjà 2020a; Skipper 2020; Tang 2020.

[o] Downgraded by one level for serious risk of bias: all trials except Skipper 2020 were open-label. Chen 2020a had a high risk of selection and reporting bias; Chen 2020b a high risk of performance, detection, and reporting bias and unclear risk of selection bias; Mitjà 2020a a high risk of performance, detection, attrition, and reporting bias for this outcome, and unclear risk of selection bias; Skipper 2020 a high risk of reporting bias and unclear risk of attrition bias; and Tang 2020 an unclear risk of attrition and reporting bias. We deemed Skipper 2020, Mitjà 2020a, and Tang 2020 as at high risk of other bias.

[p] Not downgraded for inconsistency: despite high statistical heterogeneity ($I^2 = 87\%$), all of the effect estimates were above a risk ratio of 1, with only one trial having a confidence interval that crossed 1.

[q] Cavalcanti 2020; Chen 2020a; Chen 2020b; Chen 2020c; Skipper 2020; Tang 2020.

[r] Downgraded by two levels for very serious imprecision: low number of events, and lower confidence interval bound represents appreciable harm from HCQ, whereas the upper bound includes appreciable benefit.

[s] Cavalcanti 2020.

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[t]Downgraded by one level for risk of bias: Cavalcanti 2020 was unblinded, which could have led to detection bias, meaning more participants with QT prolongation were identified in the HCQ group.
[u]Downgraded by one level for indirectness: Cavalcanti 2020 included only hospitalized patients, and excluded participants with severe disease, in whom problems with drug interactions and cardiac arrhythmia are more likely.
[v]Downgraded by one level for imprecision: Cavalcanti 2020 had a low event rate for this outcome, and a small sample size leading to a very broad confidence interval.

Summary of findings 2. Hydroxychloroquine (HCQ) compared to placebo for the prevention of COVID-19 in people who have been exposed to SARS-CoV-2

Patients or population: people who have been exposed to SARS-CoV-2

Settings: community

Intervention: HCQ

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with HCQ				
Development of confirmed COVID-19 at 14 days from enrolment	2 per 100	**2 per 100** (1 to 6)	**RR 1.20** (0.50 to 2.87)	821 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of HCQ on development of confirmed COVID-19 at 14 days from enrolment.
Hospitalized due to COVID-19[c]	2 per 1000	**2 per 1000** (0 to 31)	**RR 0.98** (0.06 to 15.66)	821 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of HCQ on risk of being hospitalized due to COVID-19.
Participants with any adverse events	17 per 100	**41 per 100** (31 to 53)	**RR 2.39** (1.83 to 3.11)	700 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	HCQ probably increases the risk of adverse events when compared with placebo.
Participants with serious adverse events	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	700 (1 RCT)	⊕⊕◯◯ LOW [a,d]	HCQ may result in little or no difference in serious adverse events when compared with placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HCQ:** hydroxychloroquine; **RCT:** randomized controlled trial; **RR:** risk ratio.

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GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded by one level for serious indirectness: one trial, limited to North America; few older and comorbid participants, possibly due to social media-based recruitment and internet-based data collection (Boulware 2020).
[b]Downgraded by two levels for very serious imprecision: confidence interval around effect estimate includes appreciable benefit and appreciable harm.
[c]This outcome, as reported by Boulware 2020, was closest to our predefined outcome of 'disease severity of participants who develop COVID-19, as defined by study authors'.
[d]Downgraded by one level for imprecision: no events in either group, therefore risk ratio is not estimable. The optimal information size to be confident that this is a true reflection of risk of serious adverse events would be larger than the total number of participants in this trial. Risk difference = 0% (95% CI −1% to 1%).

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BACKGROUND

Description of the condition

Coronavirus disease 2019 (COVID-19) is a viral infection transmitted by respiratory droplet spread. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 commonly presents as a mild respiratory tract illness, with fever and cough the most commonly reported symptoms; however, in some people this progresses to cause a life-threatening respiratory syndrome (Guan 2020).

SARS-CoV-2 is a novel coronavirus that has caused a pandemic since December 2019. Over 27 million people have been diagnosed with COVID-19, and as of 7 September 2020 over 890,000 people have died (JHU 2020). The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on 30 January 2020, and a pandemic on 11 March 2020 (WHO 2020a).

National data from China and Italy describe severe disease in 14% to 20% of people with COVID-19, and a further 2% to 5% are reported to have critical illness (ISS 2020; Wu 2020). Early mortality estimates ranged from around 2% to 12%, though this has varied considerably between countries and as the pandemic has progressed (ISS 2020; Wu 2020). Severe disease is characterized by hypoxia, and progressive acute respiratory distress syndrome appears to be the driver for mortality, although patients can experience a syndrome with clinical and laboratory features of severe systemic inflammation, termed a "cytokine storm" (Guan 2020; Mehta 2020).

At the other end of the spectrum, asymptomatic infection is not uncommon; national Italian data describe this in approximately 10% of all people with a confirmed COVID-19 diagnosis (ISS 2020). More recently, wide-ranging longer-term morbidity has been described in the absence of a severe initial illness (Greenhalgh 2020).

Transmission is by direct contact with people with the infection, indirectly via contact with respiratory secretions on objects and surfaces, or from droplets generated by sneezing and coughing (WHO 2020b). Concerns have been raised about airborne transmission: viability of SARS-CoV-2 has been demonstrated for at least three hours when suspended in an aerosol (van Doremalen 2020). The amount of virus found in the respiratory tract appears to be higher in people with severe versus those with mild disease, with shedding of virus in the nasopharynx occurring for up to 25 days in people with severe disease (Liu 2020a). The virus has also been found in stools, with one study reporting live virus in non-diarrhoeal stool, thus raising concerns about faecal-oral transmission (Wang 2020a).

Multiple episodes of transmission by pre-symptomatic or asymptomatic people have been described (Bai 2020; Rothe 2020).

The main method for diagnosis of COVID-19 is by polymerase chain reaction (PCR) of respiratory tract samples, mostly from the nasopharynx or oropharynx. However, some guidelines advise nasal swabs (CDC 2020), and some evidence suggests lower respiratory samples, such as sputum, may have higher sensitivity (Wang 2020a). Serological tests are being used for detecting antibodies to SARS-CoV-2 for confirmation of past infection, although there are concerns regarding the evidence for their accuracy and value in certain populations and clinical situations (Deeks 2020).

Transmission is common in, though not limited to, households (Pung 2020). Self-isolation, quarantine, and travel restrictions can limit community transmission (Kraemer 2020), but prevention measures within households can be more challenging. Healthcare workers are at high risk of being infected. Data from Italy show that 20% of frontline healthcare workers responding to the pandemic have developed COVID-19 (Lancet 2020). There were widespread shortages of personal protective equipment (Lewis 2020). With established community transmission in many countries, healthcare workers are also at risk outside of health facilities. Despite vaccine roll-out having commenced in some countries, achieving target coverage will take several months, and will not eliminate symptomatic infections in the near future. Consequently, there is great interest in using existing drugs as treatment for or prevention of COVID-19.

Several potential antivirals have been suggested for use in treating people with COVID-19. Remdesivir, a drug trialled for Ebola virus disease and Middle East respiratory syndrome (MERS), showed promising results in vitro (Wang 2020b). An early trial showed no benefit on time to clinical improvement, mortality, or clearance of the virus from the respiratory tract (Wang 2020c). Subsequently, two randomized trials have reported a beneficial effect of remdesivir on measures of clinical improvement in patients hospitalized with COVID-19, but no significant effect on mortality (Beigel 2020; Spinner 2020). Other experimental antivirals being studied include the influenza treatments umifenovir (Arbidol), Deng 2020, and favipiravir, Cai 2020, and the antiretroviral protease inhibitor combination lopinavir/ritonavir (Cao 2020). Of the many other options being investigated, corticosteroids are now recommended by WHO for patients with COVID-19 requiring oxygen or higher respiratory support therapy (WHO 2020d), having been reported to reduce mortality in this population in a systematic review (REACT 2020). Other options that have yet to show benefit in randomized trials are tocilizumab (Stone 2020), convalescent plasma (Agarwal 2020), and camostat mesylate (Hoffman 2020). Several studies have used novel methods to assess whether existing drugs can be repurposed for COVID-19 treatment (Chandel 2020; Zhou 2020).

Description of the intervention

Chloroquine (CQ) and hydroxychloroquine (HCQ) are 4-aminoquinoline compounds, derivatives of quinine, and have been used as antimalarial drugs since the 1940s (Ben-Zvi 2012). HCQ is an analogue of CQ in which one of the N-ethyl substituents of CQ is β-hydroxylated. HCQ and CQ have similar pharmacokinetic properties, with high oral bioavailability and tissue penetrance, partial hepatic metabolism, and high volumes of distribution as they diffuse into adipose tissue (Ben-Zvi 2012).

Both drugs have been used widely and for many years for the treatment and prevention of malaria (although they are now largely ineffective against falciparum malaria) and in the treatment of rheumatological conditions, such as systemic lupus erythematosus and rheumatoid arthritis (Fiehn 2020; Steinhardt 2011).

The mechanism of action in malaria is thought to result from inhibition of the biocrystallization of hemozoin, causing cytotoxic accumulation of heme (Schrezenmeier 2020). For rheumatological conditions, the mechanism of action is not fully delineated, but appears to arise from multiple effects. As weak bases, both CQ and HCQ accumulate in the acidic environment within lysosomes,

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and thus interfere with lysosomal activity and autophagy, which in turn may inhibit major histocompatibility complex (MHC) class II expression and antigen presentation, inhibiting immune activation (Schrezenmeier 2020). CQ and HCQ also interfere with Toll-like receptor (TLR) signalling, again via changes to local pH but also through direct binding to nucleic acids. TLR signal pathways stimulate cytokine production, and CQ and HCQ have been demonstrated to inhibit production of various cytokines including interleukin (IL)-1, IL-6, tumour necrosis factor (TNF), and interferon gamma (IFNγ) by mononuclear cells (van den Borne 1997).

CQ and HCQ have well-described adverse effect profiles. Common adverse effects include gastrointestinal upset and headache (Ben-Zvi 2012). Several adverse effects are associated with chronic therapy, such as QT-interval prolongation on electrocardiogram, other cardiac arrhythmia, and retinopathy (Fiehn 2020). CQ is generally less tolerable than HCQ, and can cause acute poisoning at a lower dose, as has been seen in reports from the USA and Nigeria of members of the public taking CQ without a prescription (CNN 2020; Owens 2020).

There are two types of CQ salts: CQ phosphate and CQ sulphate. Most dosing recommendations for CQ refer to the salt rather than the base compound. Usual doses for CQ are 250 mg to 500 mg CQ phosphate (155 mg to 310 mg CQ base) per dose, or CQ sulphate 200 mg (150 mg CQ base), with weekly dosing for malaria prophylaxis, and daily dosing for treatment of malaria and rheumatological conditions. HCQ is given at a dose of 400 mg weekly for malaria prophylaxis, and 200 mg to 400 mg daily for rheumatological disease (Ben-Zvi 2012).

How the intervention might work

Some researchers have suggested that both CQ and HCQ could be clinically effective against COVID-19. Studies have reported in vitro activity against SARS-CoV-2 (Liu 2020b; Wang 2020b; Yao 2020), and pharmacokinetic modelling suggests efficacy of a few postulated dosing regimens for treatment (Yao 2020).

Liu 2020b reported that CQ and HCQ appear to inhibit transport of SARS-CoV-2 virions from early endosomes to endolysosomes in Vero E6 cells, which may be a requirement for release of the viral genome and subsequent viral replication. Wang 2020b performed a "time-to-addition" assay using Vero E6 cells and found that CQ appeared to both inhibit entry of SARS-CoV-2 into cells and inhibit viral replication after cell entry. The authors of both studies also speculate that CQ and HCQ could impact on disease severity in COVID-19 through modulating the excess cytokine release that appears to contribute to life-threatening forms of the disease (Liu 2020b; Wang 2020b).

Why it is important to do this review

Given the pace of the pandemic, and the extraordinary impact on public health and society in many countries, there is high demand for effective prevention and treatment interventions for COVID-19. CQ and HCQ are inexpensive drugs that are registered in most countries, and are included on the WHO essential medicines list (WHO 2019). They can be delivered orally, and both drugs have well-described safety profiles in adults and children. Given the uncertain effects of antiviral drugs for treatment of COVID-19, or the effectiveness of the newly developed vaccines, identifying existing medicines that may be of benefit is of high importance. Despite the small number of published studies, some governments have recommended using HCQ as prophylaxis for healthcare workers, and some prominent political figures have asserted that CQ or HCQ should be used as a first-line treatment for COVID-19. Sadly, there have already been instances of significant harm where individuals have misinterpreted news stories about the use of CQ and suffered toxicity as a result (CNN 2020).

CQ and HCQ for treatment of COVID-19

Earlier national guidelines, mostly in February to April 2020, recommended CQ or HCQ for the treatment of individuals with COVID-19. Belgian guidelines recommended HCQ for severe disease, and advised that it be considered for mild-moderate disease (WIV-ISP 2020). Chinese guidelines advised consideration of CQ in all hospitalized patients, although later iterations have expressed caution regarding dosing and special patient groups (Wong 2020). Italian guidelines recommended early use of CQ or HCQ, or lopinavir/ritonavir (Brescia-COVID Group 2020). More recently, concerns about adverse effects have led to removal of recommendations to use CQ and HCQ from several national guidelines, alongside which the US Food and Drug Administration revoked their initial emergency use authorization provided for use of CQ and HCQ in the treatment of COVID-19 (FDA 2020), and the UK Medicines and Healthcare products Regulatory Agency enforced suspension of recruitment to trial arms using CQ or HCQ as an intervention (Robinson 2020).

Initial observational studies reported efficacy of CQ and HCQ. A widely publicized small, non-randomized study from Marseille, France, reported that HCQ was associated with earlier negative PCR for SARS-CoV-2 among 20 patients given HCQ compared to those who had refused to take HCQ or who had presented to other hospitals (Gautret 2020a). Subgroup analyses reported quicker clearance of the virus for six participants who had azithromycin in combination with HCQ versus those who received neither drug (Gautret 2020a). There has been widespread criticism of the methods, reporting, and conclusions of this study (Machiels 2020). The same group then published two observational single-arm cohorts of patients treated with HCQ plus azithromycin, reporting benefit of the combination (Gautret 2020b; Million 2020). Soon after this, another research group from France reported much poorer clinical and virological outcomes in 11 hospitalized patients treated with both drugs (Molina 2020). A quasi-experimental study of patients admitted with moderate COVID-19 in four French hospitals reported no difference in efficacy outcomes, but reported early discontinuation of HCQ in 9 of 84 participants due to abnormalities on electrocardiography (Mahévas 2020).

More recently, a number of larger non-randomized studies have reported beneficial effects of HCQ. A retrospective cohort study in Michigan, USA compared four groups of a total of 2541 patients hospitalized with confirmed COVID-19 according to physician-directed treatment assignment: 1202 received HCQ; 147 azithromycin alone; 783 HCQ with azithromycin; and 409 received neither drug (Arshad 2020). A significant reduction in mortality was reported when HCQ was received (hazard ratio (HR) 0.49, 95% confidence interval (CI) 0.29 to 0.83). Differences in baseline characteristics suggested underlying confounding, although an underpowered propensity-matching analysis reported persistence of the reported mortality benefit (Arshad 2020). The quantity of missing data and early patient exclusions were not reported

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(Arshad 2020). Another study retrospectively comparing 4542 patients in Belgian hospitals reported lower risk of death in the group who received HCQ as per national guidance (804/4542, 17.7%) versus 3533 patients who did not receive HCQ (957/3533, 27.1%) (Catteau 2020). After adjusting for multiple covariates, this difference was found to be statistically significant (adjusted HR 0.68, 95% CI 0.62 to 0.76) (Catteau 2020). Of note, nearly 50% of patients screened for eligibility were excluded, though some of these patients were found to have similar baseline characteristics to those included in the analysis (Catteau 2020).

At the time of writing the protocol for this review, China had reported two small randomized trials of HCQ, with mixed results (Chen 2020a; Chen 2020b). Several trials have since been reported and are included in this review.

CQ and HCQ for preventing COVID-19

Despite no human data on prophylaxis early in the pandemic, the Indian Council of Medical Research (ICMR) recommended HCQ as pre-exposure prophylaxis for frontline healthcare workers having “high-risk” contact with patients with suspected or confirmed COVID-19, and postexposure prophylaxis for household and healthcare worker contacts of patients with confirmed COVID-19 (ICMR 2020). The background section of this recommendation referred to in vivo evidence for efficacy of HCQ for the treatment of COVID-19, and inferred prophylactic efficacy from therapeutic efficacy (ICMR 2020). Concerns have been raised by multiple groups regarding this approach (Rathi 2020).

Since then, two comparative studies have reported the effect of use of CQ or HCQ for prophylaxis of COVID-19, one of which is a randomized trial (Boulware 2020), and the other a case-control study conducted by the ICMR (Chatterjee 2020). The former is included in this review. The case-control study involved a telephone survey of healthcare workers tested for SARS-CoV-2 when suspected of having symptomatic COVID-19: the 378 cases (172 of whom took HCQ) had a positive PCR test for SARS-CoV-2, whilst 373 controls (193 of whom used HCQ) had a negative test (Chatterjee 2020). Whilst use of HCQ versus no use of HCQ was not found to be significantly associated with confirmed COVID-19, a dose-response effect was reported, with lower odds of positive PCR the higher the number of weekly doses reported to have been taken: for four or five maintenance doses of HCQ after an initial loading dose, the adjusted odds ratio using multivariate regression analysis was 0.44 (95% CI 0.22 to 0.88) (Chatterjee 2020). Reported side effects were uncommon. Methods were reported incompletely, such as the sampling approach for cases and controls from the database of 21,402 healthcare workers, of whom 1073 has a positive PCR test (Chatterjee 2020). The target sample size was not met, though this was calculated for HCQ prophylaxis as a binary exposure variable, rather than the duration-based groups used in the eventual analysis (Chatterjee 2020). Several trials exploring the use of CQ or HCQ for prophylaxis of COVID-19 are ongoing (Cortegiani 2020).

Adverse events have been a particular concern with CQ and HCQ. Studies using data from pharmacovigilance databases prior to the use of these drugs, and azithromycin, have suggested caution regarding even short-term use due to their association with cardiac adverse effects (Nguyen 2020; Singh 2020). A randomized trial comparing higher-dose CQ (41 participants) versus lower-dose CQ (40 participants) in patients hospitalized with severe COVID-19 in northern Brazil was stopped early by the independent safety monitoring board due to higher death and cardiac serious adverse events, including QT-interval prolongation on electrocardiogram, in the group receiving higher-dose CQ (Borba 2020). An article published in *The Lancet* reporting higher incidence of death and serious adverse events in patients receiving CQ or HCQ with or without a macrolide drug (azithromycin or clarithromycin), as documented in a large international surgical registry. *The Lancet* later retracted this when the data and analysis were questioned, though regulatory authorities and trial steering groups had already decided to stop trials or trial arms investigating CQ and HCQ (Mehra 2020).

At the time of development of the protocol for this review, other systematic reviews had already been produced. Due to the intense interest in finding a therapeutic that is safe and effective for COVID-19, many review papers have been published over the last six months. Reviews published early in the outbreak relied on pre-clinical data, expert commentary, and small, mostly non-randomized studies. A systematic review of CQ for the treatment of COVID-19, which searched PubMed and Embase up to 1 March 2020, identified no published studies other than the aforementioned letter (Gao 2020), though 23 clinical trials of CQ or HCQ were found on registries (Cortegiani 2020). Another systematic review of CQ and HCQ for treating COVID-19, published as a preprint on 30 March 2020, concluded: “There is theoretical, experimental, preclinical and clinical evidence of the effectiveness of chloroquine in patients affected with COVID-19” (Kapoor 2020). A further review included one non-randomized study and one randomized trial, and concluded: "Without further evidence, HCQ is not appropriate for patients with COVID-19 in primary care" (McCormack 2020). A systematic review of antimalarials (CQ and HCQ) for the treatment of COVID-19 was produced by the Epistemonikos Working Group, which synthesized the results of two small randomized trials and found low- to very low-certainty evidence regarding efficacy and harms (Epistemonikos 2020).

We propose that, in this context, a systematic review of randomized controlled trials using standard Cochrane methods that provides summary estimates of effects for both treatment and prophylactic use of CQ and HCQ, with an appraisal of the certainty of the evidence using the GRADE approach, is important for the general public, clinicians, and policymakers. We plan to update this review in an expedited fashion as new data become available from the trials that are currently in progress on prevention.

OBJECTIVES

To evaluate the effects of chloroquine (CQ) or hydroxychloroquine (HCQ) as:

1. an antiviral treatment on death and time to clearance of the virus from clinical samples in people with COVID-19;
2. a prophylactic treatment on prevention of COVID-19 in people at risk of SARS-CoV-2 exposure;
3. a prophylactic treatment on prevention of COVID-19 in people who have been exposed to SARS-CoV-2.

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METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

Objective 1. People who have COVID-19, as defined by study authors.

Objective 2. People who are at risk of SARS-CoV-2 exposure, as defined by study authors.

Objective 3. People who have been exposed to SARS-CoV-2, as defined by study authors.

Types of interventions

Intervention

Chloroquine (CQ) or hydroxychloroquine (HCQ) given by any route of administration and dose used alone or in combination with other treatments.

Control

No treatment, supportive treatment, or other experimental antiviral treatment (i.e. any other treatment that does not contain CQ or HCQ).

Types of outcome measures

Objective 1. For treatment of COVID-19 disease

Primary outcomes

- Death
- Time to negative PCR for SARS-CoV-2 on respiratory samples

Secondary outcomes

- Number of participants admitted to hospital (if receiving ambulatory treatment)
- Number of participants requiring mechanical ventilation
- Length of hospital admission
- Time to clinical improvement, as defined by study authors
- Duration of mechanical ventilation postenrolment in survivors of COVID-19

Objectives 2 and 3. For prevention of COVID-19 disease in people at risk of exposure/who have been exposed to SARS-CoV-2

Primary outcomes

- Development of confirmed COVID-19, as defined by study authors
- Production of antibodies to SARS-CoV-2

Secondary outcomes

- Development of COVID-19 in household contacts of the recipient of the prophylaxis
- Disease severity of participants who develop COVID-19, as defined by study authors

Adverse events (relating to objectives 1, 2, and 3)

- All adverse events
- All serious adverse events attributed to study drug (i.e. serious adverse effects)
- QT-interval prolongation

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress) up to 15 September 2020.

Electronic searches

We searched the following databases on 15 September 2020 using the search terms and strategy described in Appendix 1: the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library, up to Issue 9 of 12, September 2020; MEDLINE (PubMed) (1966 to 15 September 2020); and Embase (1974 to 15 September 2020). We also searched Current Controlled Trials (www.controlled-trials.com) and the World Health Organization International Clinical Trials Registry Platform (www.who.int/clinical-trials-registry-platform) using 'chloroquine', 'hydroxychloroquine', 'coronavirus', and 'COVID-19' as search terms on 15 September 2020. We also searched COVID-specific resources COVID-NMA (www.covid-nma.com) and the Cochrane COVID-19 Study Register (covid-19.cochrane.org/), which are updated daily with lists of ongoing and published trials, using 'chloroquine' and 'hydroxychloroquine' on 15 September 2020.

Searching other resources

We contacted researchers in the field to identify any unpublished or ongoing studies.

Data collection and analysis

Two review authors (BS and HR, MC, or TK) independently conducted each step of study selection and data extraction. Any disagreements were resolved through discussion.

Selection of studies

Two review authors (BS and HR or MC) independently screened the search results using Covidence (Covidence), and retrieved the full-text articles of all potentially relevant trials. We examined each trial report to ensure that we included multiple publications from the same trial only once. We planned to contact trial authors for clarification if eligibility of a trial was unclear. Any disagreements were resolved through discussion. We listed the excluded studies and the reasons for their exclusion in the 'Characteristics of excluded studies' table. The study selection process is illustrated in a PRISMA diagram (Figure 1).

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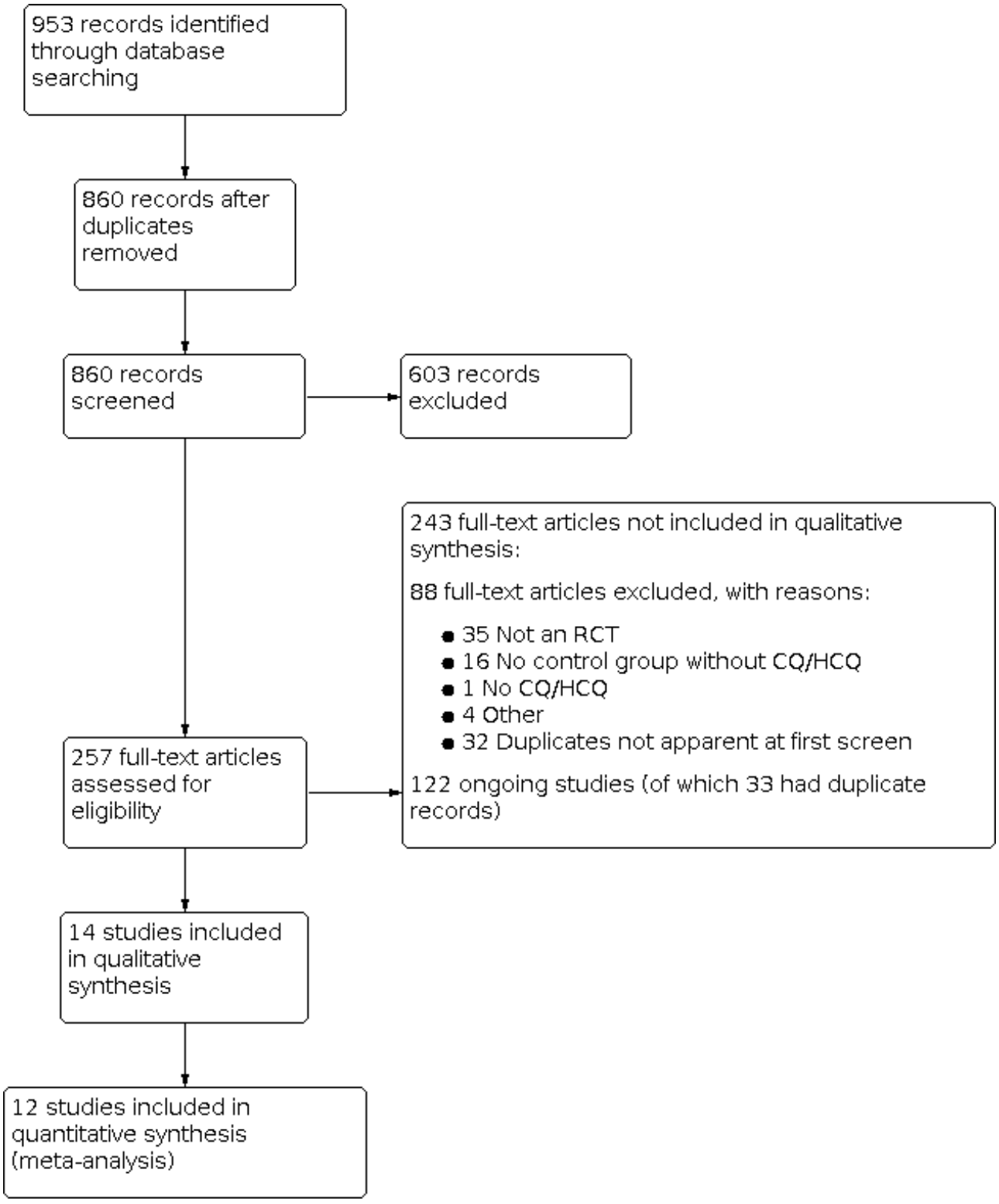
Figure 1. Study flow diagram.



Data extraction and management

Two review authors (BS and HR, MC, or TK) used a piloted data extraction form to extract data on participant characteristics, diagnostic criteria, disease severity, comorbidity, CQ or HCQ dose and administration, other treatments given, and outcome measures. Any disagreements were resolved through discussion. We contacted the corresponding trial author in the case of unclear or missing data.

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For dichotomous outcomes, we recorded the number of participants that experienced the event and the number of participants randomized to each treatment group. We recorded the number of participants analysed in each treatment/prophylaxis arm, and used the discrepancy between the figures to calculate the number of participants lost to follow-up, which would allow us to perform sensitivity analyses to investigate the effect of missing data if necessary. For continuous outcomes, we planned to extract means for the outcome in each group; we also recorded medians for narrative comparisons where means were unavailable.

Assessment of risk of bias in included studies

Two review authors (BS and HR, MC, or TK) assessed the methodological quality of studies using the Cochrane 'Risk of bias' tool, and reported the results in a 'Risk of bias' figure (Higgins 2011). We classified each 'Risk of bias' domain as either at high, low, or unclear risk of bias (Higgins 2011). We assessed the risk of bias associated with blinding for each outcome separately and used these judgements in the GRADE assessment, but made an overall judgement in the 'Risk of bias' assessment for each study based on the primary outcome as stated by the study authors. For other domains we assessed the risk of bias for the trial as a whole. We planned to attempt to contact the trial authors if information was not specified or was unclear. Any disagreements were resolved by discussion between the review authors.

Measures of treatment effect

We presented dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CIs). We reported continuous outcomes as mean differences (MD) with 95% CIs if the outcomes were measured in the same way across all included trials. If included trials measured continuous outcomes in different ways, we would use the standardized mean difference (SMD) and 95% CI as the effect measure. If using the SMD, we would re-express the SMD in the units of one or more of the specific measurement instruments used in the original studies, to aid interpretation. We presented time-to-event outcomes as hazard ratios (HRs) and 95% CIs.

Unit of analysis issues

We did not anticipate that any cluster-randomized studies would meet our inclusion criteria. In the case that cluster-randomized studies did meet our inclusion criteria, we would ensure appropriate analysis adjusting for the effect of cluster randomization was carried out before including effects estimates in a meta-analysis. If available, we planned to extract adjusted measures of effect from the trial reports. If only unadjusted data were available, we would adjust these data ourselves using the intracluster correlation coefficient (ICC). If the ICC was not reported, we would contact the study authors to obtain it, or borrow an ICC value from a similar study, or estimate the ICC. If the ICC was estimated, we would perform sensitivity analyses to investigate the robustness of our analyses.

If we identified multi-arm trials, we would either select relevant arms for inclusion in our analyses, or if more than two arms were relevant to this review, we would either combine intervention arms so that there was one comparison, or split the control group between multiple comparisons so that participants are not double-counted in meta-analysis.

We did not anticipate that any cross-over trials for treatment of COVID-19 would meet our inclusion criteria, as cross-over trials are used to evaluate interventions that have a temporary effect in the treatment of stable, chronic conditions.

We also thought it unlikely that cross-over trials would have been conducted for the prevention of COVID-19, due to the long half-life of CQ/HCQ, meaning that a long wash-out period would be required. It is also unknown whether the effects of receiving CQ or HCQ in the first period of the trial may have an irreversible effect that would subsequently impact outcomes in the second period of the trial. If we identified cross-over trials for the prevention of COVID-19, we would include data from the first period of the trial only. We would carefully consider whether studies that reported data only for the first period of a cross-over trial were at risk of bias, and whether the omission of studies that did not report data from the first period of the trial (i.e. only a paired analysis was reported) would lead to bias at the meta-analysis level.

Dealing with missing data

The primary analysis for efficacy outcomes was an available-case analysis where the denominator is the number of patients completing follow-up to the point of outcome assessment, where possible. Where this was not possible, we performed an intention-to-treat analysis, with investigation of the effects of missing data. For safety outcomes, we planned to include all participants receiving at least one dose of the intervention drug or placebo.

We planned to carry out sensitivity analyses to explore the impact of missing data on the primary outcomes. For dichotomous outcomes, we planned to vary the event rate within the missing patients from intervention and control groups within plausible limits. For continuous data, we planned to also perform sensitivity analyses using the methods described by Ebrahim 2013 and Ebrahim 2014.

Assessment of heterogeneity

We assessed heterogeneity by visually inspecting the forest plots to determine closeness of point estimates with each other and overlap of CIs. We used the Chi^2 test with a P value of 0.10 to indicate statistical significance, and the I^2 statistic to measure heterogeneity. We used the following ranges outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to interpret the I^2 statistic (Higgins 2019):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We also considered the magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test), when determining the importance of the observed I^2 value.

Assessment of reporting biases

We planned to construct a funnel plot to investigate any potential reporting bias if 10 or more studies were included for a given outcome.

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Data synthesis

We analysed the data using Review Manager Web (RevMan Web 2019). We performed all meta-analyses using random-effects models. Where a meta-analysis was not appropriate due to important clinical or methodological heterogeneity, or if study results differed to the extent that combining them in a pooled analysis would not make sense, we summarized data in tables.

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by performing the following subgroup analyses for people with COVID-19.

- Disease severity at presentation
- Time in the illness when treatment started (< 7 days, and ≥ 7 days after symptoms started)
- Comorbidity, such as cardiovascular disease, diabetes, and immunosuppression
- Age
- Sex
- Admitted to hospital versus receiving ambulatory/outpatient treatment
- CQ or HCQ dosing regimen

We planned to investigate heterogeneity by performing the following subgroup analyses for people exposed to SARS-CoV-2 or at risk of exposure to SARS-CoV-2.

- Healthcare workers
- Household contacts
- Laboratory staff
- Age
- Comorbidity, such as cardiovascular disease, diabetes, and immunosuppression

Sensitivity analysis

To explore the possible effect of losses to follow-up on the effect estimates for the primary outcomes, we planned to perform sensitivity analyses. For dichotomous outcomes, we planned to vary the event rate within the missing patients from intervention and control groups within plausible limits. For continuous data, we planned to perform sensitivity analyses using the methods described by Ebrahim 2013 and Ebrahim 2014.

Summary of findings and assessment of the certainty of the evidence

We summarized the results of the analysis in 'Summary of findings' tables, and presented the summary effects estimates for the primary outcomes and other important outcomes with illustrative comparative risks. We used the GRADE framework to evaluate the certainty of evidence for each outcome, as developed by the GRADE Working Group and described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

RESULTS

Description of studies

Results of the search

Our searches identified 953 records, 93 of which were excluded as duplicate records. Of the remaining 860 records, we excluded 603 based on the assessment of titles and abstracts. We retrieved 257 full-text publications to assess for inclusion. The screening process is illustrated in a flow diagram in Figure 1.

Ongoing studies

From our search on 15 September 2020 and reviewing the COVID-NMA website, we identified 122 ongoing trials registered for treatment or prevention of COVID-19. Due to the pressures of the pandemic and fluctuating interest in CQ and HCQ, many trials have been suspended or terminated, or had significant changes in protocol. We have therefore presented a summary of those ongoing trials that are reported to be recruiting actively, or that have completed recruitment but are yet to publish, and have a target recruitment of 500 or more participants, in tables (Table 1 for 22 ongoing treatment trials; Table 2 for 15 ongoing prevention trials). Up-to-date lists of ongoing trials can be found at www.covid-nma.com, updated daily.

Included studies

We included 14 RCTs with a total of 11,915 participants. Further details of the trials are provided in subsections for each of the review's objectives. A summary description is provided in Table 3, with more details in the Characteristics of included studies section.

Objective 1. For treatment of COVID-19 disease

We included 12 RCTs (8569 participants) assessing treatment of patients diagnosed with COVID-19.

Trial size

Trial size varied widely, from 22 participants in Huang 2020 to 4716 participants in Horby 2020. Five trials recruited fewer than 100 participants each (Chen 2020a; Chen 2020b; Chen 2020c; Davoodi 2020; Huang 2020).

Geographical location and time period

Four trials were conducted in China, early in the pandemic; all completed recruitment in February 2020 (Chen 2020a; Chen 2020b; Huang 2020; Tang 2020). The other trials recruited from March until May or June 2020: in Brazil (Cavalcanti 2020); Egypt (Abd-Elsalam 2020); Iran (Davoodi 2020); Spain (Mitjà 2020a); Taiwan (Chen 2020c); the UK (Horby 2020); the USA and Canada (Skipper 2020; around 90% of participants were in the USA); and one trial recruited participants in 30 countries globally (Pan 2020).

Participants

None of the trials recruited children. The protocol of one trial was modified on 9 May 2020 to allow recruitment of children, but none of the participants in the study arms included in this review (i.e. HCQ and standard care) were children (Horby 2020). The average age in most trials was between 40 and 50 years old, except for Horby 2020, in which the mean age of participants was around 65 years in both arms, and Pan 2020, with a median somewhere between 50 and 69 years old.

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Nine trials recruited hospitalized patients (Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020b; Chen 2020c; Horby 2020; Huang 2020; Pan 2020; Tang 2020), whilst the other three trials were focused on ambulatory care and only included outpatients (Davoodi 2020; Mitjà 2020a; Skipper 2020).

Overall, 7347/8569 (85.7%) participants had COVID-19 confirmed by SARS-CoV-2 PCR on clinical samples. Six trials recruited participants only if they had a positive PCR (Chen 2020a; Chen 2020b; Chen 2020c; Huang 2020; Mitjà 2020a; Tang 2020). In three of the remaining six trials, the majority of participants had a positive PCR: 504/665 (75.8%; Cavalcanti 2020), 4234/4716 (89.8%; Horby 2020), and 1850/1853 (> 99%; Pan 2020). Skipper 2020 reported 169/491 (34.4%) to have positive PCR testing, though the test result was pending for 48/491 (9.8%), and not available or not done for 204/491 (41.5%) (Skipper 2020). Abd-Elsalam 2020 and Davoodi 2020 did not report number of participants with positive PCR test results.

Where severity of COVID-19 disease at enrolment was not reported using author label or defined criteria equivalent to asymptomatic, mild, moderate, severe or critical, this was inferred using classification as described by WHO guidance (WHO 2020c). Of the 1800 participants (9 trials) amenable to classification, 100 (6%) were asymptomatic, 1183 (66%) had mild disease, 506 (28%) moderate disease, and 11 (0.6%) severe disease. Participants in Horby 2020 were classified according to receipt of oxygen or other respiratory support: 1112/4716 (24%) were not receiving oxygen or ventilation at enrolment (who would be labelled as asymptomatic or mild); 2811/4716 (60%) received oxygen (who could have moderate, severe or critical disease, depending on oxygen needs); and 793/4716 (17%) received invasive ventilation (who would be classified as having critical disease). Participant disease severity was reported similarly by Pan 2020: 686/1853 (37%) were not receiving oxygen at enrolment; 1000/1853 (54%) were receiving oxygen or other respiratory support but not invasive ventilation; 167/1853 (9%) were receiving invasive ventilation.

Where reported, hypertension was usually the most common comorbidity, though its prevalence varied widely: from 6% of participants in Tang 2020 and 11% in Skipper 2020, to 27% in Chen 2020a and 39% in Cavalcanti 2020. The next most common comorbidity was usually diabetes mellitus, though its prevalence varied from < 10% (Chen 2020a; Huang 2020; Skipper 2020), to 19% in Cavalcanti 2020, 21% in Pan 2020, and 27% in Davoodi 2020 and Horby 2020. In three of the five trials reporting chronic heart and lung disease (including asthma), prevalence for each was < 15% of participants (Cavalcanti 2020; Mitjà 2020a; Skipper 2020); Horby 2020 reported 26% of participants to have heart disease and 22% chronic lung disease; Pan 2020 reported 21% of participants to have cardiac disease and 12% chronic lung disease or asthma. Other reported comorbidities were present in < 5% of participants, such as cancer and chronic renal or liver disease. Two of the three outpatient-treatment trials reported proportions of participants with no known comorbidities: 47% for Mitjà 2020a and 31% for Skipper 2020. The third outpatient-treatment trial reported 28% of participants to have diabetes mellitus, and 1 of 54 participants had underlying lung disease (Davoodi 2020). Two trials did not report comorbid conditions for their participants (Chen 2020b; Chen 2020c).

Special patient populations were not commonly recruited. Most trials excluded pregnant women (Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020b; Chen 2020c; Huang 2020; Mitjà 2020a; Tang 2020). Whilst not excluding pregnant women from their trials, Horby 2020 and Pan 2020 did not report how many pregnant women were included, and Skipper 2020 recruited none. Only Skipper 2020 reported recruitment of people with immunosuppression other than due to HIV (3 of 491 total participants); across all trials, 26 participants were reported to have HIV.

Two trials provided a breakdown of contact history: 238/293 (81%) had healthcare exposure history and 2% were household contacts in Mitjà 2020a; 51% of participants in Skipper 2020 were healthcare workers, whilst 29% had household exposure to someone with COVID-19.

Time from onset of symptoms to enrolment varied widely between trials. The outpatient trials reporting this information enrolled very soon after symptom onset, with medians of between one and two days in Skipper 2020 and three days in Mitjà 2020a. Three of the hospital-based trials recruited on average between six and nine days from onset (Cavalcanti 2020; Chen 2020a; Horby 2020). Tang 2020 enrolled at a mean of 16 to 17 days from onset, which contributed to the change in timing of their primary outcome, from negative SARS-CoV-2 PCR at 28 days to 10 days from enrolment. Huang 2020 recruited relatively early from onset, but this appeared to be earlier for the CQ arm (median 2.5 days) than for the lopinavir/ritonavir arm (6.5 days). Abd-Elsalam 2020, Chen 2020b, Chen 2020c, Davoodi 2020, and Pan 2020 did not report time from symptom onset to enrolment.

Interventions and comparators

Four comparisons are reported for Objective 1 (see Effects of interventions), as follows.

1. HCQ versus standard care without HCQ, or placebo

Ten trials were included in this comparison (Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020b; Chen 2020c; Horby 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020). Nine trials compared HCQ to standard of care, and one trial, Skipper 2020, compared HCQ to placebo (folic acid). Two trials were multi-arm trials: Horby 2020 allocated to five arms in a 2:1:1:1:1 ratio (the control arm (standard care) was twice the size of each intervention arm), and Pan 2020 randomized to one of five arms in a 1:1:1:1:1 ratio, of which HCQ was one arm. Horby 2020 and Pan 2020 are ongoing adaptive trials that have each dropped the HCQ arm.

2. CQ versus lopinavir/ritonavir

One trial was included in this comparison (Huang 2020).

3. HCQ + azithromycin versus standard care

One trial was included in this comparison, in which participants were randomized 1:1:1 to receive HCQ, HCQ and azithromycin, or standard of care without HCQ or azithromycin (Cavalcanti 2020).

4. HCQ versus febuxostat

One trial was included in this comparison (Davoodi 2020). In this trial, febuxostat was the experimental drug of interest, and HCQ was the comparator.

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Dosing regimens for HCQ varied widely, and are summarized in Table 4. To highlight the heterogeneity of regimens between the trials, the loading daily dose on day 1 for participants in Horby 2020 and Pan 2020 (2000 mg) was equivalent to the total cumulative dose given to participants in Chen 2020a, Chen 2020b, and Davoodi 2020.

Huang 2020 administered 500 mg of CQ twice daily for 10 days to participants in the CQ arm, without a loading dose on day one, for a cumulative total dose of 10,000 mg.

Co-interventions

The pharmacological co-interventions reported per arm in the treatment trials for comparison 1 (HCQ versus standard care without HCQ or placebo) are shown in Table 5. Considerable variability in reporting was observed. The following are of particular note regarding co-interventions.

- Cavalcanti 2020 reported that fewer than 10% of participants did not receive concurrent treatment with an antiviral, antibiotic, or corticosteroid. However, corticosteroids were rarely given (13 of 448 participants).
- All participants in Chen 2020a received nebulized interferon-alpha, and the majority (22/30) received umifenovir (Arbidol). Both are postulated anti-SARS-CoV-2 drugs.
- Horby 2020 reported that a minority of participants received concurrent corticosteroids (dexamethasone) (< 10%) and azithromycin (< 20%).
- Participants initially enrolled into the HCQ arm of Mitjà 2020a received cobicistat-boosted darunavir with HCQ as a planned combination, which was stopped when its activity against SARS-CoV-2 was called into question.
- Skipper 2020 reported subgroup analyses for self-reported use of zinc and vitamin C; this was common, with ~25% and ~50% of participants reporting their use, respectively.

There did not appear to be a difference in receipt of pharmacological co-interventions between trial arms, where this information was reported. No trials reported concurrent use of remdesivir.

Follow-up

One trial measured all outcomes up to six days (Chen 2020b); six trials followed participants up until 14 to 15 days (Cavalcanti 2020; Chen 2020a; Chen 2020c; Davoodi 2020; Huang 2020; Skipper 2020); and four trials completed data collection at 28 days from enrolment (Abd-Elsalam 2020; Horby 2020; Mitjà 2020a; Tang 2020). Pan 2020 followed participants up to discharge from hospital. Two trials used telephone follow-up in place of or in addition to in-person outcome assessment (Cavalcanti 2020; Mitjà 2020a); one trial employed online surveys for enrolment and all follow-up (Skipper 2020).

Outcome measures

Our predefined primary outcomes were death and time to negative PCR for SARS-CoV-2 on respiratory samples. Ten trials reported death (Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020c; Davoodi 2020; Horby 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020).

PCR-based outcomes varied amongst the included trials. Three trials reported time to negative PCR (Abd-Elsalam 2020; Chen 2020a; Huang 2020); four trials reported negative PCR at specified time points: 7 days (Chen 2020a; Tang 2020); 10 days (Huang 2020; Tang 2020); and 14 days from enrolment (Chen 2020c; Huang 2020; Tang 2020); and the primary outcome in one trial was reduction in 'viral load' (amount of virus per swab sample) at day 3 and day 7 after enrolment (Mitjà 2020a).

Regarding our secondary outcomes, the following information was reported.

- Number of participants admitted to hospital (if receiving ambulatory treatment): this was reported by the three outpatient-based trials (Davoodi 2020; Mitjà 2020a; Skipper 2020).
- Number of participants requiring mechanical ventilation: three trials reported this outcome (Cavalcanti 2020; Horby 2020; Tang 2020).
- Length of hospital admission: this was reported as a mean by Abd-Elsalam 2020 and Cavalcanti 2020; the authors of Tang 2020 provided this upon request. Horby 2020 reported a median, but without interquartile range, and no mean. Huang 2020 provided a Kaplan-Meier chart, but no mean; however, proportion discharged by day 14 from enrolment was reported.
- Time to clinical improvement was reported as survival data only by Tang 2020. For the remaining trials, either a mean (Abd-Elsalam 2020) or median (Chen 2020a; Mitjà 2020a) was reported, and/or the definitions of time to clinical improvement were not comparable (Chen 2020a; Chen 2020b).
- Duration of mechanical ventilation postenrolment in survivors of COVID-19 was not reported by any trials.

Five of the 12 included trials did not report the number of participants experiencing any adverse events (Abd-Elsalam 2020; Chen 2020c; Davoodi 2020; Horby 2020; Pan 2020). Five, with some overlap (Abd-Elsalam 2020; Davoodi 2020; Horby 2020; Pan 2020; Skipper 2020), did not report the number of participants experiencing serious adverse events, with Skipper 2020 stating: “No serious adverse events attributable to the study drug occurred”. The remaining trials reported events without attribution to a particular drug.

Additionally, Skipper 2020 used the change in symptoms over 14 days from enrolment as their primary outcome. This differed significantly from our predefined outcomes, and was not comparable with the outcomes of other trials.

Objective 2. For prevention of COVID-19 disease in people at risk of exposure to SARS-CoV-2

No eligible trials were identified for this objective.

Objective 3. For prevention of COVID-19 disease in people who have been exposed to SARS-CoV-2

We included two trials for this objective: one with double-blind individual randomization to HCQ or placebo that enrolled 821 participants (Boulware 2020), and one open-label cluster-RCT comparing HCQ with standard care that enrolled 2525 participants (Mitjà 2020b).

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Geographical location and time period

Boulware 2020 was based in the USA and Canada, and recruited from 17 March to 6 May 2020. Mitjà 2020b recruited in Spain between 17 March and 28 April 2020.

Participants

Both trials only recruited asymptomatic people with a history of exposure to people with laboratory-confirmed COVID-19 (Boulware 2020; Mitjà 2020b).

In Boulware 2020, exposure history was most commonly in a healthcare setting (545/821, 66%), followed by household contact (245/821, 30%). The corresponding figures for Mitjà 2020b were 12% for healthcare workers and 28% household exposure; additionally, 49% worked and 13% lived in a nursing home. Exposure was deemed to be high risk (neither eye protection nor a surgical mask/respirator was worn) in 88% of participants, with 60% in Boulware 2020 wearing no personal protective equipment. Participants were enrolled at a median of three days after exposure in Boulware 2020 and four days after exposure in Mitjà 2020b.

Children were excluded. Median age was 41 years in the HCQ arm and 40 years in the placebo arm in Boulware 2020; mean age was 49 years in both the HCQ and standard care arms in Mitjà 2020b.

Most participants did not have comorbidities associated with increased risk of severe acute COVID-19. In Boulware 2020, 12% had hypertension, 8% chronic respiratory disease (mostly asthma), 3% diabetes, and < 1% reported each of heart disease, kidney disease, and cancer; 73% reported no pre-existing conditions. Mitjà 2020b reported underlying cardiovascular disease in 13% of participants, respiratory disease in 4%, metabolic disease in 8%, and some nervous system disease in 15%. HIV and non-HIV immunosuppression were reported in 1/821 and 4/821 participants, respectively (Boulware 2020). Whilst pregnant women were not excluded, their representation in the participants was not reported (Boulware 2020). Mitjà 2020b did not report on participants with HIV or other immunosuppression, nor whether pregnant women were included.

Interventions and comparators

The HCQ dosing regimen in Boulware 2020 was the same as in Skipper 2020: 1400 mg (800 mg, then 600 mg 6 to 8 hours later) on day 1, followed by 600 mg once daily for a further four days, translating to a cumulative total of 3800 mg over five days. Mitjà 2020b used the same HCQ dosing as in the paired treatment trial Mitjà 2020a: 800 mg on day 1, followed by 400 mg once daily for a further six days, for a total of 3200 mg over seven days.

The comparator in Boulware 2020 was placebo in the form of unmarked folic acid tablets, which closely resembled HCQ tablets, to be taken on the same schedule as HCQ. Mitjà 2020b used neither placebo nor an active comparator.

Follow-up

In Boulware 2020, follow-up was conducted using online surveys exclusively, with the final survey to be completed four to six weeks after enrolment. Mitjà 2020b used a combined approach of in-person visits to the participant's home on days 1 and 14, and telephone interviews on days 3, 7, and 28.

Outcome measures

Our primary outcome of development of COVID-19 was assessed at 14 days in both trials. In Boulware 2020, the definition of COVID-19 was expanded beyond confirmed (i.e. by PCR for SARS-CoV-2) to include probable COVID-19 due to difficulty accessing PCR testing, whereas in Mitjà 2020b development of COVID-19 required both symptoms and a positive PCR test. Our second primary outcome, production of antibodies to SARS-CoV-2, was assessed by Mitjà 2020b at 14 days.

A variety of secondary outcomes were measured, including hospitalization due to COVID-19, which partly addressed our outcome of disease severity in participants developing COVID-19 (Boulware 2020; Mitjà 2020b). Onward transmission to household contacts from index participants was not assessed.

Adverse events were assessed through self-reporting by participants using an online survey in Boulware 2020, and through telephone and in-person visits in Mitjà 2020b. QT prolongation was not assessed due to lack of in-person assessment (which would be necessary for electrocardiography to be performed) in Boulware 2020; there was one in-person assessment in Mitjà 2020b, but at the participant's home, where electrocardiography may not have been practical.

Excluded studies

We excluded 791 articles (see Figure 1), 88 of which were at the full-text stage (see the Characteristics of excluded studies section), for the following reasons: 35 were not RCTs; 16 lacked a control group without CQ or HCQ; one did not include mention of CQ or HCQ; 32 duplicates were found, which had not been apparent at first screening; and four were excluded for other reasons.

Risk of bias in included studies

See Characteristics of included studies, which includes a 'Risk of bias' table for each included trial. The results of the 'Risk of bias' assessments across all included trials are summarized in Figure 2.

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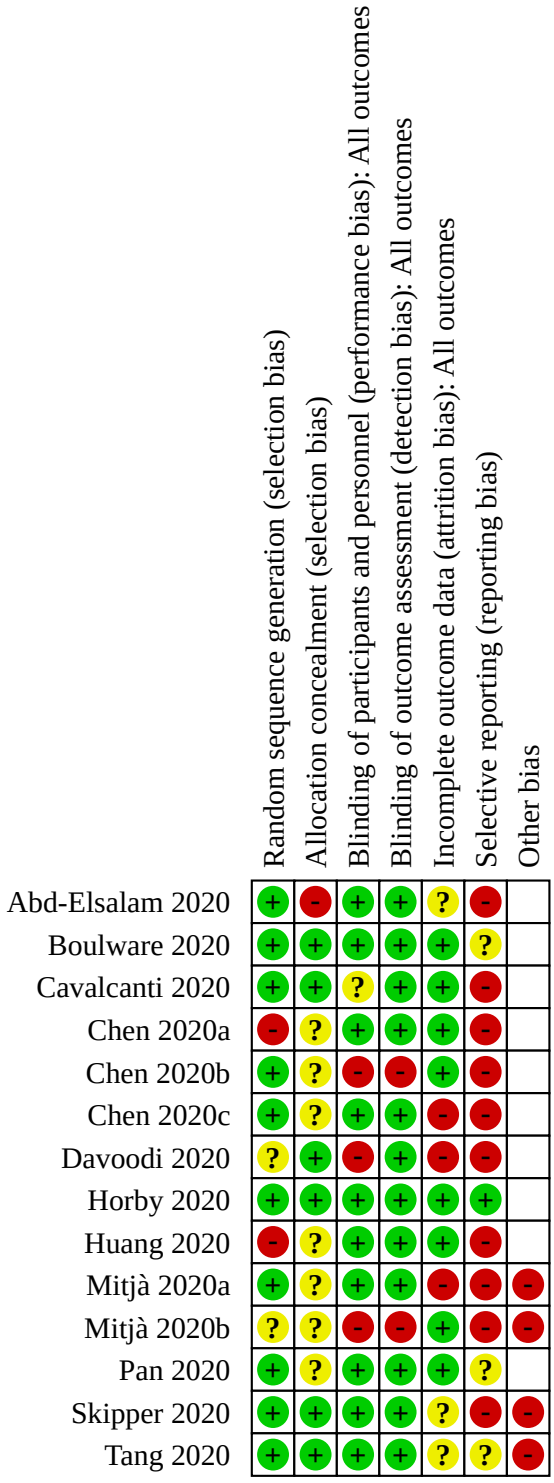
Figure 2. Risk of bias summary: review authors' judgements about each 'Risk of bias' item for each included trial.



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Allocation

We judged that 10 out of the 14 included trials were at low risk of bias (Abd-Elsalam 2020; Boulware 2020; Cavalcanti 2020; Chen 2020b; Chen 2020c; Horby 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020), two were at unclear risk of bias (Davoodi 2020; Mitjà 2020b), and two were at high risk of bias for random sequence generation (Chen 2020a; Huang 2020). The description of the method of randomisation was inadequate in Davoodi 2020 and Mitjà 2020b. Chen 2020a had 15 participants in each arm, and Huang 2020 had a notable imbalance between treatment arms raising concerns about the integrity of the randomisation process; neither trial explicitly described the method of randomisation.

We assessed six trials as at low risk of bias for allocation concealment (Boulware 2020; Cavalcanti 2020; Davoodi 2020; Horby 2020; Skipper 2020; Tang 2020), and seven trials as at unclear risk of bias due to lack of clear reporting of the method of allocation concealment (Chen 2020a; Chen 2020b; Chen 2020c; Huang 2020; Mitjà 2020a; Mitjà 2020b; Pan 2020). We judged Abd-Elsalam 2020 to be at high risk of bias for allocation concealment, as the method used was not reported, and there were more participants with comorbidity (obesity and smoking history) in the intervention arm, although there was not a statistically significant difference in these characteristics between the treatment arms.

Blinding

We assessed the risk of bias associated with blinding for each outcome separately (details are provided in the 'Risk of bias' table for each trial), but made our overall judgement for each trial based on the primary outcome as stated by the trial authors.

We assessed 10 trials as at low risk of performance bias (blinding of participants and personnel) (Abd-Elsalam 2020; Boulware 2020; Chen 2020a; Chen 2020c; Horby 2020; Huang 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020). We judged Cavalcanti 2020 to be at unclear risk of bias, as it was not blinded, and the primary outcome consisted of an ordinal scale ranking clinical improvement or deterioration. We judged Chen 2020b to be at high risk of bias because although the authors stated that the researchers and patients were unaware of treatment assignments, no placebo was used and the methods of blinding were not described, and the primary outcome was based on patient-reported clinical recovery. We judged Davoodi 2020 to be at high risk of bias as it was an open-label trial, and the primary outcome of hospitalization could have been influenced by clinicians knowing the treatment allocation. Similarly, we judged Mitjà 2020b to be at high risk of bias as it was an open-label trial, and the primary outcome involved a subjective assessment of symptoms.

We assessed 11 trials as at low risk of detection bias (blinding of outcome assessment) (Abd-Elsalam 2020; Boulware 2020; Cavalcanti 2020; Chen 2020a; Chen 2020c; Davoodi 2020; Horby 2020; Huang 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020). We judged Chen 2020b and Mitjà 2020b to be at high risk of detection bias, as the outcome assessors were not blinded to treatment allocation, and the primary outcomes of time to clinical improvement and development of symptoms are likely to have been subjectively assessed.

Incomplete outcome data

We assessed eight trials as at low risk of bias for incomplete outcome data (Boulware 2020; Cavalcanti 2020; Chen 2020a; Chen 2020b; Horby 2020; Huang 2020; Mitjà 2020b; Pan 2020). Three trials were at unclear risk of bias for this domain: Abd-Elsalam 2020 did not report on losses to follow-up or missing data; Skipper 2020 had significant losses to follow-up that were balanced between each group, but no explanations for losses were provided; and Tang 2020 had significant loss to follow-up beyond 21 days of follow-up. We assessed Mitjà 2020a as at high risk of bias for incomplete outcome data: 60 participants were excluded from the intention-to-treat (ITT) analysis due to negative baseline SARS-CoV-2 swab, missing reverse transcription polymerase chain reaction (RT-PCR) at all follow-up visits, or consent withdrawal, and a further 23 participants had protocol deviations including eight participants lost to follow-up. We judged Chen 2020c as at high risk of attrition bias, as the authors reported loss to follow-up of ~10% (3/33), and missing participants were imputed as having negative results, which could have impacted on the results as the sample size was small. We judged Davoodi 2020 as at high risk of bias as there were no outcome data for 10% (6/60), which could have impacted the results due to the small sample size.

Selective reporting

We assessed Horby 2020 as at low risk of bias for selective reporting. Three trials were at unclear risk of bias for this domain: Boulware 2020 changed the primary outcome from confirmed COVID-19 cases to probable due to a problem with access to testing; Pan 2020 was accessed as a preprint at the time of writing of this review, which did not include all outcome data, and referencing one change between protocol and trial report that was not explained; Tang 2020 changed their primary outcome and gave justification for this, but did not report the secondary outcomes. Ten trials were at high risk of bias for selective reporting (Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020b; Chen 2020c; Davoodi 2020; Huang 2020; Mitjà 2020a; Mitjà 2020b; Skipper 2020), all of which reported outcomes that deviated from those stated in the protocol (described in Characteristics of included studies).

Other potential sources of bias

We identified other potential sources of bias in four trials. Skipper 2020 and Tang 2020 were at high risk of bias as they were terminated early, which could have introduced bias as both trials had a time-updating variable as the primary outcome. Mitjà 2020a was also at high risk of other bias: a small number of participants were randomized who were in fact not eligible for the trial, but these participants were kept as part of the ITT population.

Mitjà 2020b was a cluster-randomized trial, and so was assessed for risk of bias against five further domains specific to cluster-randomized trials. We judged the trial to be at low risk for four out of five domains (see Characteristics of included studies), and at high risk of bias for comparability with individually randomized trials: contamination was possible due to the open-label design, and the intervention would be expected to work best when given to all contacts of a case rather than some being randomized to the intervention and some randomized to no intervention, which would preclude comparability with an individually randomized trial.

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Effects of interventions

See: **Summary of findings 1** Hydroxychloroquine (HCQ) compared to standard care or placebo for the treatment of people with COVID-19; **Summary of findings 2** Hydroxychloroquine (HCQ) compared to placebo for the prevention of COVID-19 in people who have been exposed to SARS-CoV-2

See Summary of findings 1 for Objective 1, Comparison 1, and Summary of findings 2 for Objective 3.

Due to inability to extract data disaggregated for subgroups on outcomes predefined in the review protocol, we did not perform subgroup analyses. Furthermore, heterogeneity in most analyses was minimal.

Objective 1. For treatment of COVID-19 disease

Comparison 1: HCQ versus standard care without HCQ or placebo

Ten trials of treatment of people with COVID-19 compared HCQ to standard care or placebo (8270 participants; Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020b; Chen 2020c; Horby 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020). The arm randomizing participants to a combination of HCQ with azithromycin in Cavalcanti 2020 was not included in this comparison, but is included in *Comparison 3* below.

Nine of the 10 trials reported death due to any cause (Abd-Elsalam 2020; Cavalcanti 2020; Chen 2020a; Chen 2020c; Horby 2020; Mitjà 2020a; Pan 2020; Skipper 2020; Tang 2020). Meta-analysis using ITT results for each trial found little or no difference between HCQ and standard care without HCQ or placebo in all-cause death (risk ratio (RR) 1.09, 95% confidence interval (CI) 0.99 to 1.19; 8208 participants; 9 RCTs; Analysis 1.1). Sensitivity analysis performed using modified ITT results as reported by three trials revealed no difference in the pooled effect estimate (RR 1.09, 95% CI 0.99 to 1.19; 8043 participants; 9 RCTs; Analysis 1.2) (Cavalcanti 2020; Mitjà 2020a; Skipper 2020).

Our predefined outcome involving tests for SARS-CoV-2, time to negative PCR for SARS-CoV-2 on respiratory samples, was reported as a median by Chen 2020a and Chen 2020c, and as a mean by Abd-Elsalam 2020 and Tang 2020; all trials reported no significant difference between the arm that received HCQ and the arm that did not. Two of the trials reported the related outcome of negative PCR for SARS-CoV-2 at day 7 after enrolment as dichotomous outcomes (Chen 2020a; Tang 2020), and three trials reported negative PCR at day 14 (Chen 2020a; Chen 2020c; Tang 2020). We deemed the latter (i.e. negative PCR at day 14) to be more important based on the current understanding of COVID-19, so this is displayed in Summary of findings 1 . No significant difference between HCQ and standard care without HCQ was revealed in meta-analysis of either negative PCR at day 14 (RR 1.00, 95% CI 0.91 to 1.10; 213 participants; 3 RCTs; Analysis 1.3) or negative PCR at day 7 (RR 0.86, 95% CI 0.68 to 1.09; 180 participants; 2 RCTs; Analysis 1.4) after enrolment.

Of the two trials assessing ambulatory treatment of people with COVID-19, only Skipper 2020 was included in the analysis of risk of admission to hospital; Mitjà 2020a did not report denominators disaggregated for allocation to HCQ versus standard care without HCQ. In Skipper 2020, though the risk ratio may suggest an important benefit from HCQ, the confidence intervals were wide, and included potential important harm (RR 0.41, 95% CI 0.13 to 1.27; 465 participants; 1 RCT; Analysis 1.5).

Three trials reported results for people hospitalized with COVID-19 going on to require mechanical ventilation (Cavalcanti 2020; Horby 2020; Tang 2020). No significant difference was found in participants progressing to mechanical ventilation when comparing HCQ to no HCQ (RR 1.11, 95% CI 0.91 to 1.37; 4521 participants; 3 RCTs; Analysis 1.6).

Three trials reported mean length of hospital admission (Abd-Elsalam 2020; Cavalcanti 2020; Tang 2020). We noted that early in the pandemic suitability for discharge was often driven by infection prevention and control considerations, and therefore might not have been a good reflection of the efficacy of HCQ. Accordingly, we decided not to include results from Tang 2020 in the analysis for this outcome, as participants remained in hospital until they were deemed no longer infectious. Pooled length of admission in Abd-Elsalam 2020 and Cavalcanti 2020 did not differ between participants who received HCQ and those who did not (mean difference (MD) 0.15 days shorter with HCQ, 95% CI 0.75 shorter to 0.45 longer; 642 participants; 2 RCTs; Analysis 1.7).

Time to clinical improvement (for symptomatic patients) and time to negative PCR for SARS-CoV-2 on respiratory samples were reported as hazard ratios (HRs) and corresponding 95% CIs by Tang 2020. No significant difference was found for time to clinical improvement (HR 1.01, 95% CI 0.59 to 1.74; 119 participants; 1 RCT; Analysis 1.8) or time to negative PCR for SARS-CoV-2 on respiratory samples (HR 0.85, 95% CI 0.58 to 1.23; 150 participants; 1 RCT; Analysis 1.9).

Duration of mechanical ventilation postenrolment in survivors of COVID-19 was not reported by any trials.

Six trials reported number of participants with any adverse events (Cavalcanti 2020; Chen 2020a; Chen 2020b; Mitjà 2020a; Skipper 2020; Tang 2020). Meta-analysis revealed a higher risk of adverse events in participants receiving HCQ versus those receiving standard care or placebo (RR 2.90, 95% CI 1.49 to 5.64; 1394 participants; 6 RCTs; Analysis 1.10). Adverse events reported in the six trials are summarized in Table 6.

Meta-analysis of six trials that reported the number of participants experiencing serious adverse events showed no significant difference between participants receiving HCQ and those receiving standard care (RR 0.82, 95% CI 0.37 to 1.79; 1004 participants; 6 RCTs; Analysis 1.11) (Cavalcanti 2020; Chen 2020a; Chen 2020b; Chen 2020c; Mitjà 2020a; Tang 2020). It was not possible to disaggregate data for specific serious adverse events for each trial, nor was it possible to disaggregate data for serious adverse events attributed to the intervention drug for each trial.

Our predefined specific adverse event, prolongation of the QT-interval on electrocardiogram (ECG), was reported by one trial (Cavalcanti 2020). Risk of QT-interval prolongation increased in participants receiving HCQ (without azithromycin) versus those receiving standard care or azithromycin (RR 8.47, 95% CI 1.14 to 63.03; 147 participants; 1 RCT; Analysis 1.12). Fewer than half of participants had an ECG performed within seven days of enrolment; this appeared to be higher in those receiving HCQ (89/199, 44.7%) than in those receiving standard care (58/177, 32.8%).

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Comparison 2: CQ versus lopinavir/ritonavir (LPV/r)

One trial (22 participants) reported this comparison (Huang 2020). Due to the comparison not having been predefined, and this being a single small trial with high risk of selection and reporting bias, reporting few of our predefined outcomes, a separate 'Summary of findings' table is not provided.

Death was not reported as an outcome (Huang 2020).

Time to negative PCR for SARS-CoV-2 on respiratory samples was not reported, but the proportion with negative PCR ranged from appreciable benefit to appreciable harm between arms at day 7 from enrolment (RR 1.20, 95% CI 0.64 to 2.25; 22 participants; 1 RCT; Analysis 2.1) and day 14 from enrolment (RR 1.08, 95% CI 0.85 to 1.36; 22 participants; 1 RCT; Analysis 2.2).

Number of participants admitted to hospital (if receiving ambulatory treatment) was not relevant for this hospital inpatient-based trial.

Number of participants requiring mechanical ventilation after enrolment was not reported (Huang 2020).

We were unable to extract length of hospital admission as a mean, but visual inspection of the Kaplan-Meier chart appeared to show a median time to discharge of around 11 days for the CQ arm, and around 14 days for the LPV/r arm (Huang 2020). The number of participants discharged by day 14 from enrolment was reported to be 10/10 in the CQ arm versus 6/12 in the LPV/r arm (RR 1.91, 95% CI 1.09 to 3.34; 22 participants; 1 RCT; Analysis 2.3).

Time to clinical improvement was not reported as a mean or median (Huang 2020). However, clinical recovery at day 10 was reported as showing no significant difference between study arms (RR 1.37, 95% CI 0.78 to 2.42; 22 participants; 1 RCT; Analysis 2.4).

There was no difference in the number of participants experiencing adverse events between study arms (RR 1.08, 95% CI 0.78 to 1.50; 22 participants; 1 RCT; Analysis 2.5); QT-interval prolongation was not specifically reported. No serious adverse events were reported in either arm (Huang 2020).

Comparison 3: HCQ + azithromycin versus standard care

One trial (444 participants) reported this comparison (Cavalcanti 2020). Due to the comparison not having been predefined, and this trial having a high risk of reporting bias and unclear risk of performance and detection bias, a separate 'Summary of findings' table is not provided.

Death was reported as showing no difference between study arms (RR 0.52, 95% CI 0.13 to 2.07; 444 participants; 1 RCT; Analysis 3.1).

Time to negative PCR for SARS-CoV-2 was not reported, and as this was a trial of hospitalized patients, neither was number of participants admitted to hospital (Cavalcanti 2020).

The number of participants requiring mechanical ventilation did not differ between study arms (RR 1.61, 95% CI 0.82 to 3.15; 444 participants; 1 RCT; Analysis 3.2). Duration of mechanical ventilation was not reported (Cavalcanti 2020).

Length of hospital admission was similar between groups (MD 0.50 days longer with HCQ + azithromycin, 95% CI 0.81 days shorter to 1.81 days longer; 444 participants; 1 RCT; Analysis 3.3).

Time to clinical improvement was not reported.

Adverse events were experienced by a higher proportion of participants who received at least one dose of HCQ + azithromycin versus participants receiving neither HCQ nor azithromycin (RR 1.74, 95% CI 1.27 to 2.38; 416 participants; 1 RCT; Analysis 3.4). Serious adverse events did not differ significantly between study arms (RR 1.85, 95% CI 0.36 to 9.43; 416 participants; 1 RCT; Analysis 3.5).

When assessed, QT-interval prolongation on ECG was more common amongst participants receiving HCQ + azithromycin (17/116) versus those receiving neither drug (1/58) (RR 8.50, 95% CI 1.16 to 62.31; 174 participants; 1 RCT; Analysis 3.6). Performance of ECG within seven days of enrolment appeared to be more frequent in the HCQ + azithromycin arm (116/239, 48.5%) than in the standard care arm (58/177, 32.8%).

Comparison 4: HCQ versus febuxostat

One trial (60 participants) reported this comparison (Davoodi 2020). A separate 'Summary of findings' table is not provided.

No deaths were reported in either study arm (Davoodi 2020).

Three participants in each arm (of 25 in the HCQ arm and 29 in the febuxostat arm) required hospitalization during the 14 days of follow-up (RR 1.16, 95% CI 0.26 to 5.24; 54 participants; 1 RCT; Analysis 4.2).

Number of participants requiring mechanical ventilation was not reported explicitly, but the authors reported: “All hospitalised patients … did not require ICU care" (Davoodi 2020).

Length of hospital admission was not reported precisely, but authors reported: “All hospitalised patients were released from hospitals between 1 and 7 days of hospitalization” (Davoodi 2020).

Time to clinical improvement was not reported in a way that fit with our planned data extraction or analysis.

Duration of mechanical ventilation was not reported.

Reduction in involvement of the lungs on CT scan between days 1 and 14 was reported to be no different between the HCQ and febuxostat arms.

Adverse events were not reported.

Objective 2. Preventing COVID-19 disease in people at risk of exposure to SARS-CoV-2

No eligible trials provided outcome results for this objective.

Objective 3. Preventing COVID-19 disease in people who have been exposed to SARS-CoV-2

We deemed the effect of HCQ on the prevention of COVID-19 to be susceptible to differences in administration to an individual, versus a cluster of individuals all in contact with one index person. We

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therefore did not pool results from the individually-randomized RCT, Boulware 2020, with those from the cluster-RCT (Mitjà 2020b).

Comparison 5: HCQ versus placebo by individual randomization

One trial (821 participants) reported this comparison (Boulware 2020). See Summary of findings 2.

Development of confirmed COVID-19 at 14 days from enrolment was not found to differ significantly between the two arms (RR 1.20, 95% CI 0.50 to 2.87; 821 participants; 1 RCT; Analysis 5.1).

Production of antibodies to SARS-CoV-2 and development of COVID-19 in household contacts of the recipient of the prophylaxis were not reported (Boulware 2020).

For our predefined outcome of disease severity of participants who develop COVID-19, we extracted data for participants hospitalized due to COVID-19; this did not differ significantly between those receiving HCQ and those receiving placebo (RR 0.98, 95% CI 0.06 to 15.66; 821 participants; 1 RCT; Analysis 5.2).

Participants receiving at least one dose of HCQ had an increased risk of adverse events compared to those not receiving HCQ (RR 2.39, 95% CI 1.83 to 3.11; 700 participants; 1 RCT; Analysis 5.3). No serious adverse events were reported in either arm. QT-interval prolongation on ECG was not reported, but follow-up was performed remotely using an online survey, so ECG was not performed as part of the trial (Boulware 2020).

Comparison 6: HCQ versus standard care by cluster randomization

One trial (2525 participants) reported this comparison (Mitjà 2020b). Due to the cluster-RCT design and appropriate analysis by the trial authors, adjusted risk ratios have been taken from the report.

Development of symptomatic confirmed COVID-19 at 14 days from enrolment was not found to differ significantly between participants randomized to HCQ (64/1116; 5.7%) and those allocated to standard care (74/1198; 6.2%) (adjusted RR 0.89, 95% CI 0.54 to 1.46; 2314 participants; 1 RCT; Mitjà 2020b).

Production of antibodies to SARS-CoV-2 at 14 days was reported in 137/958 (14.3%) of the participants in HCQ clusters and 91/1042 (8.7%) in clusters not receiving HCQ (adjusted RR 1.6, 95% CI 0.96 to 2.69; 2000 participants; 1 RCT; Mitjà 2020b).

Development of COVID-19 in household contacts of the recipient of the prophylaxis was not reported by either trial.

Disease severity of participants who developed COVID-19 was not reported. Five participants in the HCQ clusters (with a denominator of 1197, which is unexplained in its deviation from the randomized total of 1225) and 8/1300 in the standard care clusters died (Mitjà 2020b). Causes of death were not reported.

Adverse events were reported in 671/1197 (56%) participants in the HCQ clusters versus 77/1300 (6%) participants in the clusters not receiving HCQ; a relative effect estimate was not reported (Mitjà 2020b). Serious adverse events were reported, but it was not clear whether they were reported as number of events or number of participants, and did not match the intensity grading reported by the pharmacovigilance consultants employed by the trial (Mitjà 2020b). QT-interval prolongation was not measured in this trial.

DISCUSSION

Summary of main results

Treating COVID-19 disease

Ten trials compared HCQ versus standard care without HCQ, or placebo (see Summary of findings 1). HCQ makes little or no difference to death due to any cause, compared with no HCQ (high-certainty evidence). HCQ may make little or no difference to the likelihood of a negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment (low-certainty evidence). HCQ probably results in little to no difference in progression to mechanical ventilation (moderate-certainty evidence). We are very uncertain about the effect of HCQ on time to clinical improvement when compared to standard care without HCQ or placebo (very low-certainty evidence). HCQ probably results in an increased risk of developing adverse events (moderate-certainty evidence), but may make little or no difference to the risk of serious adverse events (low-certainty evidence). We are very uncertain about the effect of HCQ on prolongation of QT-interval on ECG when compared with standard care without HCQ, or placebo (very low-certainty evidence).

We have drawn no conclusions from small single-trial comparisons of CQ versus lopinavir/ritonavir; HCQ and azithromycin versus standard care; and HCQ versus febuxostat.

Objective 2. For prevention of COVID-19 disease in people at risk of exposure to SARS-CoV-2

No eligible studies were identified for this objective.

Objective 3. For prevention of COVID-19 disease in people who have been exposed to SARS-CoV-2

One individually randomized trial compared HCQ with placebo (see Summary of findings 2). We are very uncertain about the effect of HCQ on the development of confirmed COVID-19 at 14 days from enrolment and the risk of hospitalization due to COVID-19, compared with placebo (very low-certainty evidence). HCQ probably increases the risk of adverse events, compared with placebo (moderate-certainty evidence). HCQ may result in little or no difference in serious adverse events, compared with placebo, though no participants in the trial experienced any events (low-certainty evidence).

A cluster-randomized trial compared HCQ with no intervention for postexposure prevention of COVID-19. The results of this trial could not be combined with those of the individually randomized RCT. There was no difference in the risk of symptomatic confirmed COVID-19 or production of antibodies to SARS-CoV-2 between study arms.

Overall completeness and applicability of evidence

Objective 1. For treatment of COVID-19 disease

The 12 included trials were conducted in Brazil, Canada, China, Egypt, Iran, Spain, Taiwan, the UK, and the USA. The largest trial, contributing the majority of participants (4716/8569, 55%), was based in the UK. It is as yet uncertain whether geographical

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differences may impact on the efficacy or safety of interventions for the treatment of COVID-19.

None of the trials included children or pregnant women, so the evidence cannot be applied to these populations. Most participants (86%) had COVID-19 confirmed by positive RT-PCR for SARS-CoV-2. Nine of the 12 trials recruited hospitalized patients, with the three ambulatory treatment trials contributing only 844/8569 (10%) of participants in the review, potentially affecting applicability of the findings to outpatient settings.

Severity of disease varied between trials. Whilst not all participants could be classified according to WHO severity grading, 3139/8569 (37%) of participants did not require oxygen or other respiratory support at enrolment; 5230/8569 (63%) were receiving oxygen or higher respiratory support. The two largest trials (Horby 2020; Pan 2020), which mostly included participants requiring oxygen or higher respiratory support, contributed the majority of participants to the meta-analysis of the outcome death due to any cause for the comparison of HCQ versus standard care or placebo. Data for participants with any or serious adverse events could not be extracted from these trials. This means that evidence for the outcome of death was based on a population with more severe disease. For adverse events outcomes, the meta-analysed population was less severely unwell, and so this effects estimate should be interpreted with this in mind as the baseline risk of adverse events in more severely unwell patients is likely to be higher. These trials were designed to assess the efficacy of HCQ, and may not be of sufficient power to detect any but the most common adverse events.

HCQ and CQ have similar pharmacological actions, but only one study used CQ, to which 10 participants were allocated, and so we could not draw conclusions about the efficacy and safety of CQ for the treatment of COVID-19. This is likely due to the increased rate of adverse effects seen with CQ compared with HCQ in other conditions.

Only one trial included an arm with a combination of HCQ and azithromycin (217 participants), and so few conclusions can be drawn about the efficacy or safety of this combination treatment.

Dosing of HCQ varied considerably between trials (see Table 4). The two largest trials used relatively high total cumulative doses, and so it is unlikely that a lack of efficacy for the primary outcome of death is due to underdosing. As the data for adverse events were drawn from the trials using lower doses, it is possible that this meta-analysis underestimates dose-dependent adverse events.

Pharmacological co-interventions also varied considerably between studies (see Table 5), and reporting was at times incomplete. Co-interventions were mostly balanced between intervention arms across the studies, and are unlikely to have impacted on the summary effects estimates for the primary outcome.

Objective 2. For preventing COVID-19 disease in people at risk of exposure to SARS-CoV-2

No eligible studies were identified for this objective.

Objective 3. For preventing COVID-19 disease in people who have been exposed to SARS-CoV-2

One of the two trials included in this objective was conducted in the USA and Canada; the other in Spain. Most participants were healthcare or nursing home workers and had no comorbidities; average age was between 40 and 50 years. Consequently, the findings may have limited applicability of the evidence to older people with multi-morbidity, household contacts, and possibly to lower-income settings. Additionally, as the assessment for the development of COVID-19 was based on the presence of symptoms, and no outcomes assessed infection or disease in household or other contacts of the person with exposure to SARS-CoV-2, no evidence was available for the effect of HCQ on the risk of asymptomatic infection or onward transmission.

Certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence, employing GRADEpro GDT software (GRADEpro GDT). The GRADE assessment with explanatory footnotes is outlined in Summary of findings 1 and Summary of findings 2.

For Objective 1 - treatment of COVID-19, we included nine RCTs and assessed seven outcomes. We graded the effect estimate for death as high certainty, implying that treatment with HCQ results in no difference to death from any cause in people with COVID-19. We graded the effect estimate for negative SARS-CoV-2 PCR at 14 days as low certainty, that is HCQ may make no difference to the proportion of people who have a negative SARS-CoV-2 swab at 14 days; the certainty of the evidence was downgraded by one level for serious risk of bias, as both trials in this analysis were at high risk of bias across several domains; and one level for serious indirectness, as almost all participants had mild or moderate COVID-19, all were hospitalized, and all were from one country (Chen 2020a; Tang 2020). We graded the effect estimate for progression to mechanical ventilation as moderate certainty, implying that HCQ probably has no effect on progression to mechanical ventilation in people with COVID-19; the certainty of the evidence was downgraded by one level for serious imprecision, as the lower bound of the confidence interval around the estimate represents no benefit nor harm from HCQ, whereas the upper bound suggests appreciable harm. For time to clinical improvement, we graded the estimate of effect as very low certainty, that is we do not know what effect HCQ has on this outcome. Data for this outcome came from a single trial (Tang 2020); we downgraded the certainty of the evidence for serious risk of bias, serious indirectness (all hospitalized patients with mild-moderate COVID-19 in one centre in China), and serious imprecision (confidence interval extends from appreciable benefit to appreciable harm).

For adverse effects in people with COVID-19 treated with HCQ, we graded the effects estimate for participants with any adverse events as moderate certainty, meaning that HCQ probably increases the risk of developing adverse events. We downgraded the certainty of the evidence by one level for serious risk of bias, as all trials contributing to this analysis had high or unclear risk of bias across various domains, and all but one trial were open-label. We graded the effects estimate for participants with serious adverse events as low certainty, downgrading by two levels for very serious imprecision, as the confidence intervals ranged from appreciable benefit to appreciable harm; overall the rate of serious adverse events was low. We graded the effects estimate for participants

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who developed prolonged QT interval on ECG as very low certainty; data for this outcome came from one trial, and the certainty of the evidence was downgraded for risk of bias, as the trial was open-label; indirectness, as severe COVID patients were excluded; and imprecision, as the low event rate and small sample size led to a broad confidence interval.

We found no studies addressing Objective 2 - prevention of COVID-19 disease in people at risk of exposure to SARS-CoV-2.

For Objective 3 - prevention of COVID-19 in people who have been exposed to SARS-CoV-2, we included one RCT and graded four outcomes (Boulware 2020). We graded the effects estimate for development of COVID-19 at 14 days from enrolment as very low certainty, implying that we do not know whether HCQ prevents COVID-19 in people exposed to SARS-CoV-2. We downgraded the certainty of the evidence by one level for serious indirectness, as data for this outcome came from a single trial in North America with few older or comorbid participants; and by two levels for very serious imprecision, as the confidence interval around the effects estimate included appreciable benefit and appreciable harm. We graded the effect estimate for participants hospitalized due to COVID-19 as very low certainty, again downgrading by one level for serious indirectness and by two levels for very serious imprecision. We graded the effects estimate for participants with any adverse events as moderate certainty, implying that HCQ probably increases the risk of adverse events when compared with placebo; the certainty of the evidence was downgraded by one level for serious indirectness, as described above. We graded the effects estimate for participants with serious adverse events as low certainty, meaning that HCQ may result in no difference to the risk of developing serious adverse events compared with placebo; the certainty of the evidence was downgraded by one level for serious indirectness and one level for serious imprecision.

Potential biases in the review process

We took measures to limit bias in the review process by following the procedures outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). The Cochrane Infectious Diseases Group (CIDG) Information Specialist conducted the literature search using a variety of general and COVID-19 specific resources, and included preprints. In addition, we also checked the COVID-NMA website at www.covid-nma.com/ for further studies at regular intervals. We did not make a funnel plot, as fewer than 10 studies were included per comparison. Two review authors independently examined the search results, assessed studies for eligibility, and extracted data, in order to minimize bias in study selection and data extraction.

Agreements and disagreements with other studies or reviews

Several systematic reviews have been published examining the treatment of COVID-19 with HCQ/CQ, all of which have included RCTs and non-randomized studies. For the most part their conclusions match ours regarding the finding of HCQ showing no benefit for mortality from COVID-19, but with less precision. Fiolet 2020, published in August 2020, describes results from 29 studies including 3 RCTs, but studies with no mortality were excluded. In participants treated with HCQ versus comparator group for the outcome of death, the RR was 0.83 (95% CI 0.65 to 1.06); excluding non-randomized studies, the RR was 1.09 (95% CI 0.97 to 1.24). The authors concluded that HCQ is not effective for COVID-19, and that further research is not needed. Elavarasi 2020, published in September 2020, is a systematic review of RCTs, case series, and cohort studies with a comparator arm including 12 non-randomized studies and 3 RCTs. Meta-analysis of the included studies revealed no difference in mortality with HCQ use (RR 0.98 95% CI 0.66 to 1.46), leading the authors to conclude that the available evidence does not support the use of HCQ and that further RCTs are required. Hernandez 2020, published in August 2020, is a living systematic review which includes 3 RCTs, 8 cohort studies, and 3 case series. No meta-analysis was conducted due to high heterogeneity between studies; the authors concluded that the evidence on the benefits and harms of HCQ for COVID-19 is weak and conflicting. Zang 2020, published in September 2020, includes 3 RCTs, 2 prospective observational studies, and 2 retrospective observational studies. In participants treated with HCQ compared with standard therapy, meta-analysis suggested increased mortality with HCQ (RR 1.92, 95% CI 1.26 to 2.93), although the authors identified significant unexplained heterogeneity and problems with study quality, and concluded that better RCTs are urgently needed. All these systematic reviews cite the three Chinese RCTs included in this review (Chen 2020a; Chen 2020b; Tang 2020). Few systematic reviews have used GRADE to assess the certainty of the evidence.

There are fewer studies and fewer reviews examining CQ and HCQ as prophylaxis for COVID-19 (Objectives 2 and 3). Shah 2020 is a systematic review of the evidence for HCQ in preventing COVID-19, which was published in March 2020. Due to the lack of studies at that time, the authors included only two pre-clinical studies and three commentaries, concluding that although evidence from pre-clinical studies is promising, there was no evidence to support the efficacy of CQ or HCQ in preventing COVID-19.

National and international guideline recommendations for the use of CQ and HCQ have changed over the course of the pandemic. The US National Institutes of Health published updated guidance on 27 August 2020 recommending against the use of CQ or HCQ for the treatment of COVID-19 in hospitalized patients, and against the use of CQ or HCQ in non-hospitalized patients except in the context of a clinical trial (NIH 2020). In May 2020, WHO recommended that CQ and HCQ not be administered to COVID-19 patients outside of the context of a clinical trial (WHO 2020c).

AUTHORS' CONCLUSIONS

Implications for practice

Hydroxychloroquine for treatment

Hydroxychloroquine (HCQ) has no clinical benefit in treating COVID-19 in hospitalized patients, with moderate- to high-certainty evidence from several randomized trials, and a probable increase in adverse events associated with its use.

Evidence for prevention of hospital admission in outpatients with COVID-19 is very uncertain. However, given the lack of benefit in hospitalized patients, and limited available evidence suggesting little or no effect on clearance of the virus from the respiratory tract, benefit from treatment of outpatients appears unlikely.

Hydroxychloroquine for pre- or post-exposure prophylaxis

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The lack of any demonstrable clinical benefit in the treatment of COVID-19 makes it less likely the drug will prevent the illness in those who are exposed, but this effect is not excluded.

No trials of the use of HCQ for prophylaxis of COVID-19 in those at risk of exposure to SARS-CoV-2 were identified.

Evidence that HCQ is effective as prophylaxis for COVID-19 in people exposed to SARS-CoV-2 is limited. However, HCQ probably increases adverse events, although there does not appear to be a difference between comparison groups for serious adverse events.

Implications for research

No further trials in hospital inpatients are justified.

The evidence is less certain for ambulatory treatment of people with mild COVID-19, and for prevention of COVID-19 in people with, or at risk of, exposure to SARS-CoV-2.

If other reasons are identified that suggest the drugs may have benefit in prevention despite no effect in treatment, then researchers should ensure that trials are adequately powered, prioritize inclusion of people at risk for severe COVID-19, and include risk of asymptomatic infection and onward transmission as outcome measures.

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REFERENCES

References to studies included in this review

Abd-Elsalam 2020 *{published data only}*

Abd-Elsalam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, Abd El Ghafar MS, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. *American Journal of Tropical Medicine and Hygiene* 2020;**103**(4):1635-9. [DOI: 10.4269/ajtmh.20-0873]

Boulware 2020 *{published data only}*

Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *New England Journal of Medicine* 2020;**383**(6):517-25. [DOI: 10.1056/NEJMoa2016638]

Cavalcanti 2020 *{published data only}*

Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *New England Journal of Medicine* 2020;**383**:2041-52. [DOI: 10.1056/NEJMoa2019014]

Chen 2020a *{published data only}*

Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *Journal of Zhejiang University* 2020;**49**(2):215-9. [DOI: 10.3785/j.issn.1008-9292.2020.03.03]

Chen 2020b *{published data only}*

Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. www.medrxiv.org/content/10.1101/2020.03.22.20040758v2 (accessed 20 April 2020). [DOI: 10.1101/2020.03.22.20040758]

Chen 2020c *{published data only}*

Chen CP, Lin YC, Chen TC, Tseng TY, Wong HL, Kuo CY, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19). www.medrxiv.org/content/10.1101/2020.07.08.20148841v1 (accessed prior to 18 December 2020). [DOI: 10.1101/2020.07.08.20148841]

Davoodi 2020 *{published data only}*

Davoodi L, Abedi SM, Salehifar E, Alizadeh-Navaei R, Rouhanizadeh H, Khorasani G, et al. Febuxostat therapy in outpatients with suspected COVID-19: a clinical trial. *International Journal of Clinical Practice* 2020;**74**(11):e13600. [DOI: 10.1111/ijcp.13600]

Horby 2020 *{published data only (unpublished sought but not used)}*

Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: preliminary results from a multi-centre, randomized, controlled trial. www.medrxiv.org/content/10.1101/2020.07.15.20151852v1 (accessed 15 July 2020). [DOI: 10.1101/2020.07.15.20151852]

Huang 2020 *{published data only}*

Huang M, Tang T, Pang P, Li M, Ma R, Lu J, et al. Treating COVID-19 with chloroquine. *Journal of Molecular Cell Biology* 2020;**12**(4):322–5. [DOI: 10.1093/jmcb/mjaa014]

Mitjà 2020a *{published data only}*

Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. *Clinical Infectious Diseases* 2020;**ciaa1009**:ciaa1009. [DOI: 10.1093/cid/ciaa1009]

Mitjà 2020b *{published data only}*

Mitjà O, Ubals M, Corbacho M, Alemany A, Suner C, Tebe C, et al. A cluster-randomized trial of hydroxychloroquine as prevention of Covid-19 transmission and disease. www.medrxiv.org/content/10.1101/2020.07.20.20157651v1 (accessed prior to 18 December 2020). [DOI: 10.1101/2020.07.20.20157651]

Pan 2020 *{published data only (unpublished sought but not used)}*

WHO Solidarity trial consortium, Pan H, Peto R, Abdool Karim Q, Karim QA, Alejandria M, et al. Repurposed antiviral drugs for COVID-19 - interim WHO SOLIDARITY trial results. www.medrxiv.org/content/10.1101/2020.10.15.20209817v1 (accessed prior to 18 December 2020). [DOI: 10.1101/2020.10.15.20209817]

Skipper 2020 *{published data only}*

Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Annals of Internal Medicine* 2020;**173**(8):623-31. [DOI: 10.7326/M20-4207]

Tang 2020 *{published data only}*

Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;**369**:m1849. [DOI: 10.1136/bmj.m1849]

References to studies excluded from this review

Agrawal 2020 *{published data only}*

Agrawal S, Goel AD, Gupta N. Emerging prophylaxis strategies against COVID-19. *Monaldi Archives for Chest Disease* 2020;**90**(1):169-72. [DOI: 10.4081/monaldi.2020.1289]

Alia 2020 *{published data only}*

Alia E, Grant-Kels JM. Does hydroxychloroquine combat COVID-19? A timeline of evidence. *Journal of the American Academy of Dermatology* 2020;**83**(1):e33-4. [DOI: 10.1016/j.jaad.2020.04.031]

Brown 2020 *{published data only}*

Brown R. Hydroxychloroquine and “off-label” utilization in the treatment of oral conditions. *Oral Surgery, Oral Medicine, Oral*

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Pathology and Oral Radiology 2020;**129**(6):643-4. [DOI: 10.1016/j.oooo.2020.03.047]

ChiCTR2000029542 *{published data only}*

ChiCTR2000029542. Study for the efficacy of chloroquine in patients with novel coronavirus pneumonia (COVID-19). www.chictr.org.cn/showprojen.aspx?proj=48968 (first received 3 February 2020). [ChiCTR2000029542]

ChiCTR2000029609 *{published data only}*

ChiCTR2000029609. A prospective, open-label, multiple-center study for the efficacy of chloroquine phosphate in patients with novel coronavirus pneumonia (COVID-19). www.chictr.org.cn/showprojen.aspx?proj=49145 (first received 6 February 2020). [ChiCTR2000029609]

ChiCTR2000029898 *{published data only}*

ChiCTR2000029898. Evaluation the efficacy and safety of hydroxychloroquine sulfate in comparison with phosphate chloroquine in severe patients with novel coronavirus pneumonia (COVID-19): a randomized, open-label, parallel, controlled trial. www.chictr.org.cn/showprojen.aspx?proj=49482 (first received 16 February 2020). [ChiCTR2000029898]

ChiCTR2000029899 *{published data only}*

ChiCTR2000029899. Evaluation the efficacy and safety of hydroxychloroquine sulfate in comparison with phosphate chloroquine in mild and commen (sic) patients with novel coronavirus pneumonia (COVID-19): a randomized, open-label, parallel, controlled trial. www.chictr.org.cn/showprojen.aspx?proj=49536 (first received 16 February 2020). [ChiCTR2000029899]

Colson 2020a *{published data only}*

Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *International Journal of Antimicrobial Agents* 2020;**55**(3):105923. [DOI: 10.1016/j.ijantimicag.2020.105923]

Colson 2020b *{published data only}*

Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *International Journal of Antimicrobial Agents* 2020;**55**(4):105932. [DOI: 10.1016/j.ijantimicag.2020.105932]

EUCTR2020-000890-25-FR *{published data only}*

EUCTR2020-000890-25-FR. Hydroxychloroquine as a treatment for coronavirus disease COVID-19. www.clinicaltrialsregister.eu/ctr-search/search?query=EUCTR2020-000890-25-FR (first received 10 March 2020). [EUCTR2020-000890-25-FR]

EUCTR2020-001421-31-ES *{published data only}*

EUCTR2020-001421-31-ES. Clinical trial randomized, unblinded and controled for evaluation of efficacy and safety of hydroxychloroquine chemoprophylaxis against SARS-CoV-2 (COVID-19) infection in healthcare professionals. www.clinicaltrialsregister.eu/ctr-search/search?query=EUCTR2020-001421-31-ES++ (first received 7 April 2020). [EUCTR2020-001421-31-ES]

Ferner 2020 *{published data only}*

Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in Covid-19. *BMJ* 2020;**369**:m1432. [DOI: 10.1136/bmj.m1432]

Gao 2020 *{published data only}*

Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience Trends* 2020;**14**(1):72-3. [DOI: 10.5582/bst.2020.01047]

Gendrot 2020 *{published data only}*

Gendrot M, Javelle E, Clerc A, Savini H, Pradines B. Chloroquine as a prophylactic agent against COVID-19? *International Journal of Antimicrobial Agents* 2020;**55**(6):105980. [DOI: 10.1016/j.ijantimicag.2020.105980]

Heldwein 2020 *{published data only}*

Heldwein FL, Calado A. Does hydroxychloroquine prevent the transmission of COVID-19? *Annals of the Rheumatic Diseases* 2020;**79**(6):e60. [DOI: 10.1136/annrheumdis-2020-217501]

Lee 2020 *{published data only}*

Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? *International Journal of Antimicrobial Agents* 2020;**55**(6):105988. [DOI: 10.1016/j.ijantimicag.2020.105988]

Lofgren 2020 *{published data only}*

Lofgren SM, Nicol MR, Bangdiwala AS, Pastick KA, Okafor EC, Skipper CP, et al. Safety of hydroxychloroquine among outpatient clinical trial participants for COVID-19. medRxiv [preprint] 22 July 2020. [DOI: 10.1101/2020.07.16.20155531]

Nau 2020 *{published data only}*

Nau JY. Coronavirus epidemic and chloroquine controversy. *Revue Medicale Suisse* 2020;**685**:510-1.

NCT04304053 *{published data only}*

NCT04304053. Treatment of COVID-19 cases and chemoprophylaxis of contacts as prevention (HCQ4COV19). clinicaltrials.gov/ct2/show/NCT04304053 (first received 11 March 2020). [NCT04304053]

NCT04321278 *{published data only}*

NCT04321278. Safety and efficacy of hydroxychloroquine associated with azithromycin in SARS-CoV-2 virus (Coalition Covid-19 Brasil II). clinicaltrials.gov/show/NCT04321278 (first received 25 March 2020). [NCT04321278]

NCT04321993 *{published data only}*

NCT04321993. Treatment of moderate to severe coronavirus disease (COVID-19) in hospitalized patients. clinicaltrials.gov/show/NCT04321993 (first received 26 March 2020). [NCT04321993]

NCT04323527 *{published data only}*

NCT04323527. Chloroquine diphosphate for the treatment of severe acute respiratory syndrome secondary to SARS-CoV2 (CloroCOVID19). clinicaltrials.gov/ct2/show/NCT04323527 (first received 26 March 2020). [NCT04323527]

Copyright © 2021 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.

NCT04326725 *{published data only}*

NCT04326725. Proflaxis using hydroxychloroquine plus vitamins-zinc during COVID-19 pandemia. clinicaltrials.gov/show/NCT04326725 (first received 30 March 2020). [NCT04326725]

NCT04329572 *{published data only}*

NCT04329572. Efficacy and safety of hydroxychloroquine and azithromycin for the treatment of hospitalized patients with moderate to severe COVID-19. clinicaltrials.gov/show/NCT04329572 (first received 1 April 2020). [NCT04329572]

NCT04329611 *{published data only}*

NCT04329611. ALBERTA HOPE COVID-19 for the prevention of severe COVID19 disease. clinicaltrials.gov/ct2/show/NCT04329611 (first received 1 April 2020). [NCT04329611]

NCT04332094 *{published data only}*

NCT04332094. Clinical trial of combined use of hydroxychloroquine, azithromycin, and tocilizumab for the treatment of COVID-19 (TOCOVID). clinicaltrials.gov/show/NCT04332094 (first received 2 April 2020). [NCT04332094]

NCT04333225 *{published data only}*

NCT04333225. Hydroxychloroquine in the prevention of COVID-19 infection in healthcare workers. clinicaltrials.gov/show/NCT04333225 (first received 3 April 2020). [NCT04333225]

NCT04334512 *{published data only}*

NCT04334512. A study of quintuple therapy to treat COVID-19 infection. clinicaltrials.gov/show/NCT04334512 (first received 6 April 2020). [NCT04334512]

NCT04335084 *{published data only}*

NCT04335084. A study of hydroxychloroquine, vitamin C, vitamin D, and zinc for the prevention of COVID-19 infection (HELPCOVID-19). clinicaltrials.gov/show/NCT04335084 (first received 6 April 2020). [NCT04335084]

NCT04341493 *{published data only}*

NCT04341493. Hydroxychloroquine vs nitazoxanide in patients with COVID-19. clinicaltrials.gov/show/NCT04341493 (first received 10 April 2020). [NCT04341493]

NCT04341727 *{published data only}*

NCT04341727. Hydroxychloroquine, hydroxychloroquine, azithromycin in the treatment of SARS CoV-2 infection (WU352). clinicaltrials.gov/show/NCT04341727 (first received 10 April 2020). [NCT04341727]

NCT04343092 *{published data only}*

NCT04343092. Efficacy of ivermectin as add on therapy in COVID-19 patients. clinicaltrials.gov/show/NCT04343092 (first received 13 April 2020). [NCT04343092]

NCT04343677 *{published data only}*

NCT04343677. Military COVID-19 hydroxychloroquine pre-exposure and post-exposure prophylaxis study. Unable to access - removed from clinicaltrials.gov website. [NCT04343677]

NCT04344457 *{published data only}*

NCT04344457. Evaluate the efficacy and safety of oral hydroxychloroquine, indomethacin and zithromax in subjects with mild symptoms of COVID-19. clinicaltrials.gov/ct2/show/NCT04344457 (first received 14 April 2020). [NCT04344457]

NCT04345419 *{published data only}*

NCT04345419. A real-life experience on treatment of patients with COVID 19. clinicaltrials.gov/show/NCT04345419 (first received 14 April 2020). [NCT04345419]

NCT04345653 *{published data only}*

NCT04345653. Hydroxychloroquine as chemoprevention for COVID-19 for high risk healthcare workers. clinicaltrials.gov/show/NCT04345653 (first received 14 April 2020). [NCT04345653]

NCT04346147 *{published data only}*

NCT04346147. Clinical trial to evaluate efficacy of 3 types of treatment in patients with pneumonia by COVID-19 (Covid-19HUF). clinicaltrials.gov/ct2/show/NCT04346147 (first received 15 April 2020). [NCT04346147]

NCT04347798 *{published data only}*

NCT04347798. IMPACT: IMPact of Antimalarials on Covid-19 Infections in RAPPORT (IMPACT). clinicaltrials.gov/ct2/show/NCT04347798 (first received 15 April 2020). [NCT04347798]

NCT04348474 *{published data only}*

NCT04348474. Efficacy and safety of hydroxychloroquine and azithromycin for the treatment of ambulatory patients with mild COVID-19. clinicaltrials.gov/ct2/show/NCT04348474 (first received 16 April 2020). [NCT04348474]

NCT04350281 *{published data only}*

NCT04350281. Double therapy with IFN-beta 1b and hydroxychloroquine. clinicaltrials.gov/show/NCT04350281 (first received 17 April 2020). [NCT04350281]

NCT04350450 *{published data only}*

NCT04350450. Hydroxychloroquine treatment of healthcare workers with COVID19 illness at Montefiore. clinicaltrials.gov/show/NCT04350450 (first received 17 April 2020). [NCT04350450]

NCT04351620 *{published data only}*

NCT04351620. High-dose hydroxychloroquine for the treatment of ambulatory patients with mild COVID-19. clinicaltrials.gov/show/NCT04351620 (first received 17 April 2020). [NCT04351620]

NCT04351919 *{published data only}*

NCT04351919. Assessment of efficacy and safety of HCQ and antibiotics administrated to patients COVID19(+). clinicaltrials.gov/show/NCT04351919 (first received 17 April 2020). [NCT04351919]

NCT04354870 *{published data only}*

NCT04354870. COVID-19 PrEP HCW HCQ Study. clinicaltrials.gov/ct2/show/NCT04354870 (first received 21 April 2020). [NCT04354870]

Copyright © 2021 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.

NCT04361461 *{published data only}*

NCT04361461. Use of hydroxychloroquine alone or associated for inpatients with SARS-CoV-2 virus (COVID-19). clinicaltrials.gov/ct2/show/NCT04361461 (first received 24 April 2020). [NCT04361461]

NCT04362189 *{published data only}*

NCT04362189. Efficacy and safety study of allogeneic HB-adMSCs for the treatment of COVID-19. clinicaltrials.gov/ct2/show/NCT04362189 (first received 24 April 2020). [NCT04362189]

NCT04370262 *{published data only}*

NCT04370262. Multi-site adaptive trials for COVID-19. clinicaltrials.gov/ct2/show/NCT04370262 (first received 30 April 2020). [NCT04370262]

NCT04395768 *{published data only}*

NCT04395768. International ALLIANCE study of therapies to prevent progression of COVID-19. clinicaltrials.gov/ct2/show/NCT04395768 (first received 20 May 2020). [NCT04395768]

Pagliano 2020 *{published data only}*

Pagliano P, Piazza O, De Caro F, Ascione T, Filippelli A. Is hydroxychloroquine a possible postexposure prophylaxis drug to limit the transmission to healthcare workers exposed to coronavirus disease 2019? *Clinical Infectious Diseases* 2020;**71**(15):887-8. [DOI: 10.1093/cid/ciaa320]

Patri 2020 *{published data only}*

Patrì A, Fabbrocini G. Hydroxychloroquine and ivermectin: a synergistic combination for COVID-19 chemoprophylaxis and treatment? *Journal of the American Academy of Dermatology* 2020;**82**(6):e221. [DOI: 10.1016/j.jaad.2020.04.017]

Principi 2020 *{published data only}*

Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. Lancet Infectious Diseases 17 April 2020 [Epub ahead of print]. [DOI: 10.1016/S1473-3099(20)30296-6]

Rathi 2020 *{published data only}*

Rathi S, Ish P, Kalantri A, Kalantri S. Hydroxychloroquine prophylaxis for COVID-19 contacts in India. *Lancet Infectious Diseases* 2020;**20**(10):1118-9. [DOI: 10.1016/S1473-3099(20)30313-3]

Sahraei 2020 *{published data only}*

Sahraei Z, Shabani M, Shokouhi S, Saffaei A. Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. *International Journal of Antimicrobial Agents* 2020;**55**(4):105945. [DOI: 10.1016/j.ijantimicag.2020.105945]

Yu 2020 *{published data only}*

Yu B, Li C, Chen P, Li J, Jiang H, Wang DW. Beneficial effects exerted by hydroxychloroquine in treating COVID-19 patients via protecting multiple organs. Science China Life Sciences 2020 Aug 3 [Epub ahead of print]. [DOI: 10.1007/s11427-020-1782-1]

Additional references

Agarwal 2020

Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ* 2020;**371**:m3939. [DOI: 10.1136/bmj.m3939]

Arshad 2020

Arshad S, Kilgore P, Chaudhry ZS, Jacobsen G, Wang DD, Huitsing K, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *International Journal of Infectious Diseases* 2020;**97**:396-403. [DOI: 10.1016/j.ijid.2020.06.099]

Bai 2020

Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA* 2020;**323**(14):1406-7. [DOI: 10.1001/jama.2020.2565]

Beigel 2020

Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - final report. *New England Journal of Medicine* 2020;**383**:1813-26. [DOI: 10.1056/NEJMoa2007764]

Ben-Zvi 2012

Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: from malaria to autoimmunity. *Clinical Reviews in Allergy & Immunology* 2012;**42**(2):145-53. [DOI: 10.1007/s12016-010-8243-x]

Borba 2020

Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Network Open* 2020;**3**(4):e208857. [DOI: 10.1001/jamanetworkopen.2020.8857]

Brescia-COVID Group 2020

Brescia-COVID Group. Brescia-COVID Respiratory Severity Scale Algorithm. Step-wise management approach to COVID-19 patients based on clinical severity as of March 27, 2020. www.mdcalc.com/brescia-covid-respiratory-severity-scale-bcrss-algorithm (accessed 6 April 2020).

Cai 2020

Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering 2020 March 18 [Epub ahead of print]. [DOI: 10.1016/j.eng.2020.03.007]

Cao 2020

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine 2020 March 18 [Epub ahead of print]. [DOI: 10.1056/NEJMoa2001282]

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Catteau 2020

Catteau L, Dauby N, Montourcy M, Bottieau E, Hautekiet J, Goetghebeur E, et al. Low-dose hydroxychloroquine therapy and mortality in hospitalized patients with COVID-19: a nationwide observational study of 8075 participants. *International Journal of Antimicrobial Agents* 2020;**56**(4):106144. [DOI: 10.1016/j.ijantimicag.2020.106144]

CDC 2020

Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons for Coronavirus Disease 2019 (COVID-19). www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html (accessed 20 April 2020).

Chandel 2020

Chandel V, Raj S, Rathi B, Kumar D. In silico identification of potent COVID-19 main protease inhibitors from FDA approved antiviral compounds and active phytochemicals through molecular docking: a drug repurposing approach. www.preprints.org/manuscript/202003.0349/v1 (accessed 6 April 2020). [DOI: 10.20944/preprints202003.0349.v1]

Chatterjee 2020

Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S, et al. Healthcare workers & SARS-CoV-2 infection in India: a case-control investigation in the time of COVID-19. *Indian Journal of Medical Research* 2020;**151**:459-67. [DOI: 10.4103/ijmr.IJMR_2234_20]

CNN 2020

Busari S, Adebayo B, CNN. Nigeria records chloroquine poisoning after Trump endorses it for coronavirus treatment. edition.cnn.com/2020/03/23/africa/chloroquine-trump-nigeria-intl/index.html.

Cortegiani 2020

Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. Journal of Critical Care 2020 March 10 [Epub ahead of print]. [DOI: 10.1016/j.jcrc.2020.03.005]

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 6 April 2020. Melbourne, Australia: Veritas Health Innovation, Updated on 4 February 2019. Available at covidence.org.

Deeks 2020

Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, et al. Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database of Systematic Reviews* 2020, Issue 6. Art. No: CD013652. [DOI: 10.1002/14651858.CD013652]

Deng 2020

Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, et al. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study. Journal of Infection 2020 March 11 [Epub ahead of print]. [DOI: 10.1016/j.jinf.2020.03.002]

Ebrahim 2013

Ebrahim S, Akl EA, Mustafa RA, Sun X, Walter SD, Heels-Ansdell D, et al. Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers. *Journal of Clinical Epidemiology* 2013;**66**(9):1014-21.e.1. [DOI: 10.1016/j.jclinepi.2013.03.014]

Ebrahim 2014

Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD, et al. Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. *Journal of Clinical Epidemiology* 2014;**67**(5):560-70. [DOI: 10.1016/j.jclinepi.2013.11.014]

Elavarasi 2020

Elavarasi A, Prasad M, Seth T, Sahoo RK, Madan K, Nischal N, et al. Chloroquine and hydroxychloroquine for the treatment of COVID-19: a systematic review and meta-analysis. *Journal of General Internal Medicine* 2020;**35**(11):3308-14. [DOI: 10.1007/s11606-020-06146-w]

Epistemonikos 2020

Epistemonikos COVID-19 LOVE Working Group. Antimalarials for the treatment of COVID-19: systematic review - preliminary report. Last update: 31 March 2020. www.epistemonikos.cl/2020/03/27/systematic-review-preliminary-report-antimalarials-for-the-treatment-of-covid-19/ (accessed 7 April 2020).

FDA 2020

US Food and Drug Administration. FDA News Release: Coronavirus (COVID-19) Update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and (accessed 8 September 2020).

Fiehn 2020

Fiehn C, Ness T, Weseloh C, Specker C, Hadjiski D, Detert J, et al. Safety management in treatment with antimalarials in rheumatology. Interdisciplinary recommendations on the basis of a systematic literature review. Zeitschrift fur Rheumatologie 2020 March 31 [Epub ahead of print]. [DOI: 10.1007/s00393-020-00785-4]

Fiolet 2020

Fiolet T, Guihur A, Rebeaud M, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis. *Clinical Microbiology and Infection* 2020;**27**(1):138-40. [DOI: 10.1016/ j.cmi.2020.08.022]

Gautret 2020a

Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents 2020 March 20 [Epub ahead of print]. [DOI: 10.1016/j.ijantimicag.2020.105949]

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Gautret 2020b

Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. Travel Medicine and Infectious Disease 2020;**34**:101663. [DOI: 10.1016/j.tmaid.2020.101663]

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 8 Nov 2020. Hamilton (ON): McMaster University (developed by Evidence Prime), 2020. Available from gradepro.org.

Greenhalgh 2020

Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020;**370**:m3026. [DOI: 10.1136/bmj.m3026]

Guan 2020

Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine 2020 Feb 28 [Epub ahead of print]. [DOI: 10.1056/NEJMoa2002032]

Hernandez 2020

Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or chloroquine for treatment or prophylaxis of COVID-19. Living systematic review. *Annals of Internal Medicine* 2020;**173**(4):287-96.

Higgins 2019

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Hoffman 2020

Hoffman M, Kleine-Weber H, Schroeder S, Krüger N, Herrier T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;**181**(2):271-280.e.8. [DOI: 10.1016/j.cell.2020.02.052]

ICMR 2020

Indian Council of Medical Research – National Taskforce for COVID-19. Recommendation on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM_V2.pdf (accessed 6 April 2020).

ISS 2020

Istituto Superiore di Sanità. Sorveglianza integrata COVID-19 in Italia. www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati (accessed 6 April 2020).

JHU 2020

Dong E, Du H, Gardner L, on behalf of Johns Hopkins University Center for Systems Science and Engineering. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infectious Diseases* 2020;**20**(5):533-4. [DOI: 10.1016/S1473-3099(20)30120-1]

Kapoor 2020

Kapoor KM, Kapoor A. Role of chloroquine and hydroxychloroquine in the treatment of COVID-19 infection - a systematic literature review. www.medrxiv.org/content/10.1101/2020.03.24.20042366v1 (accessed 6 April 2020). [DOI: 10.1101/2020.03.24.20042366]

Kraemer 2020

Kraemer MUG, Yang C-H, Gutierrez B, Wu C-H, Klein B, Pigott DM, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. Science 2020;**368**(6490):493-7. [DOI: 10.1126/science.abb4218]

Lancet 2020

Lancet. COVID-19: protecting health-care workers. *Lancet* 2020;**395**(10228):922. [DOI: 10.1016/S0140-6736(20)30644-9]

Lewis 2020

Lewis D. Is the coronavirus airborne? Experts can't agree. www.nature.com/articles/d41586-020-00974-w (accessed 6 April 2020). [DOI: 10.1038/d41586-020-00974-w]

Liu 2020a

Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infectious Diseases 2020 March 19 [Epub ahead of print]. [DOI: 10.1016/S1473-3099(20)30232-2]

Liu 2020b

Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discovery* 2020;**6**:16. [DOI: 10.1038/s41421-020-0156-0]

Machiels 2020

Machiels JD, Bleeker-Rovers CP, Ter Heine R, Rahamat-Langendoen J, de Mast Q, Ten Oever J, et al. Reply to Gautret et al: hydroxychloroquine sulfate and azithromycin for COVID-19: what is the evidence and what are the risks? *International Journal of Antimicrobial Agents* 2020;**56**(1):106056. [DOI: 10.1016/j.ijantimicag.2020.106056]

Mahévas 2020

Mahévas M, Tran VT, Roumier M, Chabrol A, Paule R, Guillaud C, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 2020;**369**:m2328. [DOI: 10.1136/bmj.m1844]

McCormack 2020

McCormack J, Lindblad AJ. Hydroxychloroquine with or without azithromycin for COVID-19. gomainpro.ca/tools-for-practice/articles/details/?id=619&page-title=Hydroxychloroquine+with+or+without+azithromycin+for+COVID-19 (accessed 7 April 2020).

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Mehra 2020

Mehra MR, Ruschitzka F, Patel AN. Retraction - Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020;**395**(10240):1820. [DOI: 10.1016/S0140-6736(20)31324-6]

Mehta 2020

Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;**395**(10229):1033-4. [DOI: 10.1016/S0140-6736(20)30628-0]

Million 2020

Million M, Lagier JC, Gautret P, Colson P, Fournier PE, Amrane S, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: a retrospective analysis of 1061 cases in Marseille, France. *Travel Medicine and Infectious Disease* 2020;**35**:101738. [DOI: 10.1016/j.tmaid.2020.101738]

Molina 2020

Molina JM, Delaugerre C, Le Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Médecine et Maladies Infectieuses 2020 March 30 [Epub ahead of print]. [DOI: 10.1016/j.medmal.2020.03.006]

Nguyen 2020

Nguyen LS, Dolladille C, Drici MD, Fenioux C, Alexandre J, Mira JP, et al. Cardiovascular toxicities associated with hydroxychloroquine and azithromycin: an analysis of the World Health Organization Pharmacovigilance Database. *Circulation* 2020;**142**(2):303-5. [DOI: 10.1161/CIRCULATIONAHA.120.048238]

NIH 2020

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. www.covid19treatmentguidelines.nih.gov/ (accessed 9 September 2020).

Owens 2020

Owens B. Excitement around hydroxychloroquine for treating COVID-19 causes challenges for rheumatology. Lancet Rheumatology 2020 April 1 [Epub ahead of print]. [DOI: 10.1016/S2665-9913(20)30089-8]

Pung 2020

Pung R, Chiew CJ, Young BE, Chin S, Chen MI-C, Clapham HE, et al. Investigation of three clusters of COVID-19 in Singapore: implications for surveillance and response measures. *Lancet* 2020;**395**(10229):1039-46. [DOI: 10.1016/S0140-6736(20)30528-6]

REACT 2020

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020 Sep 2 [Epub ahead of print]. [DOI: 10.1001/jama.2020.17023]

RevMan Web 2019 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). The Cochrane Collaboration, 2019. Available at: revman.cochrane.org.

Robinson 2020

Robinson J. MHRA instructs all UK hydroxychloroquine COVID-19 clinical trials to suspend recruitment. Pharmaceutical Journal 2020;**305**(7939):online (no pagination). [DOI: 10.1211/PJ.2020.20208075]

Rothe 2020

Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV Infection from an asymptomatic contact in Germany. *New England Journal of Medicine* 2020;**382**:970-1. [DOI: 10.1056/NEJMc2001468]

Schrezenmeier 2020

Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nature Reviews. Rheumatology* 2020;**16**(3):155–66. [DOI: 10.1038/s41584-020-0372-x]

Shah 2020

Shah S, Das S, Jain A, Misra DP, Negi VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). *International Journal of Rheumatic Diseases* 2020;**23**(5):613-9.

Singh 2020

Singh AP, Tousif S, Umbarkar P, Lal H. A pharmacovigilance study of hydroxychloroquine cardiac safety profile: potential implication in COVID-19 mitigation. *Journal of Clinical Medicine* 2020;**9**(6):1867. [DOI: 10.3390/jcm9061867]

Spinner 2020

Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA* 2020;**324**(11):1048-57. [DOI: 10.1001/jama.2020.16349]

Steinhardt 2011

Steinhardt LC, Magill AJ, Arguin PM. Review: Malaria chemoprophylaxis for travelers to Latin America. *American Journal of Tropical Medicine and Hygiene* 2011;**85**(6):1015–24. [DOI: 10.4269/ajtmh.2011.11-0464]

Stone 2020

Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with covid-19. *New England Journal of Medicine* 2020;**383**:2333-44. [DOI: 10.1056/NEJMoa2028836]

van den Borne 1997

van den Borne BE, Dijkmans BA, de Rooij HH, le Cessie S, Verweij CL. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. *Journal of Rheumatology* 1997;**24**(1):55-60. [PMID: 9002011]

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van Doremalen 2020

van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *New England Journal of Medicine* 2020;**382**(16):1564-7. [DOI: 10.1056/NEJMc2004973]

Wang 2020a

Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. Journal of the American Medical Association 2020 March 11 [Epub ahead of print]. [DOI: 10.1001/jama.2020.3786]

Wang 2020b

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* 2020;**30**(3):269–71. [DOI: 10.1038/s41422-020-0282-0]

Wang 2020c

Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;**395**:1569-78. [DOI: 10.1016/S0140-6736(20)31022-9]

WHO 2019

World Health Organization. WHO Model List of Essential Medicines, 21st List. www.who.int/medicines/publications/essentialmedicines/en (accessed 21 April 2020).

WHO 2020a

World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 76. www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (accessed 6 April 2020).

WHO 2020b

World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19) (accessed 6 April 2020).

WHO 2020c

World Health Organization. Clinical management of COVID-19: interim guidance 27 May 2020. www.who.int/publications/i/item/clinical-management-of-covid-19 (accessed prior to 18 December 2020).

WHO 2020d

World Health Organization. Corticosteroids for COVID-19: Living Guidance. www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 (accessed prior to 18 December 2020). [WHO REFERENCE: WHO/2019-nCoV/Corticosteroids/2020.1]

WIV-ISP 2020

WIV-ISP (Scientific Institute of Public Health, Belgium). Interim clinical guidance for adults with suspected or confirmed COVID-19 in Belgium. epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf (accessed 6 April 2020).

Wong 2020

Wong YK, Yang J, He K. Caution and clarity required in the use of chloroquine for COVID-19. Lancet Rheumatology 2020 April 2 [Epub ahead of print]. [DOI: 10.1016/S2665-9913(20)30093-X]

Wu 2020

Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;**323**(13):1239-42. [DOI: 10.1001/jama.2020.2648]

Yao 2020

Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases 2020 March 9 [Epub ahead of print]. [DOI: 10.1093/cid/ciaa237]

Zang 2020

Zang Y, Han X, He M, Shi J, Li Y. Hydroxychloroquine use and progression or prognosis of COVID-19: a systematic review and meta-analysis. *Naunyn-Schmiedeberg's Archives of Pharmacology* 2020;**Sep 6**:1-8. [DOI: 10.1007/s00210-020-01964-5]

Zhou 2020

Zhou Y, Hou Y, Shen J, Huang Y, Martin Y, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery* 2020;**6**:14. [DOI: 10.1038/s41421-020-0153-3]

References to other published versions of this review

Singh 2020a

Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No: CD013587. [DOI: 10.1002/14651858.CD013587]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abd-Elsalam 2020

Study characteristics

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Abd-Elsalam 2020 *(Continued)*

Methods	Open-label trial comparing HCQ with standard care without HCQ for the treatment of COVID-19. No placebo was used. Follow up for 4 weeks from enrolment.
Participants	Setting: 3 tertiary hospitals in Egypt. Number of participants: 194 total, 97 allocated to HCQ; 97 allocated to standard care Inclusion criteria: "all patients admitted with SARS-CoV-2 infection". Note that no criteria for diagnosis were reported. Exclusion criteria: "allergy or contraindication to HCQ, pregnant and lactating females, and patients with cardiac problem (chronic heart failure or prolonged QT interval on ECG)". Age: HCQ arm: Mean 40.35 ± SD 18.65 years; standard care arm: Mean 41.09 ± SD 20.07 years. Sex: HCQ arm: female:male 41:56; standard care arm: female:male 39:58. Method of diagnosis: not reported. Clinical presentation: not reported. COVID-19 disease severity at diagnosis: “The patients were randomized equally between the two groups regarding the disease severity”. Time from symptom onset to enrolment: not reported. Comorbidities: 1. Obesity: HCQ 40/97 (41%); standard care 35/97 (36%) 2. Morbid obesity: HCQ 21/97 (22%); standard care 24/97 (25%) 3. Smoking: HCQ 35/97 (36%); standard care 25/97 (26%) 4. Liver disease: HCQ 0/97; standard care 2/97 (2%) 5. Renal impairment: HCQ 2/97 (2%); standard care 4/97 (4%) 6. "Comorbidities": HCQ 15/97 (15%); standard care 12/97 (12%) Place of care: inpatients in hospital.
Interventions	HCQ group received 400 mg twice daily on day 1, then 200 mg twice daily up to 15 days. Control group received standard care, without HCQ.
Outcomes	Primary endpoint in the report was “percentage of recovery”. This was used for a retrospective power calculation. On ClinicalTrials.gov (clinicaltrials.gov/ct2/show/NCT04353336), primary outcomes were: • number of patients with cure or death; • number of patients with virological cure. Note that the only primary outcome on the original registry entry (17 April 2020) was number of patients with virological cure. No secondary outcomes in registry entry.
Notes	Dates of recruitment: March 2020 to June 2020. Funding and sponsorship: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Abd-Elsalam 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Computerized random number generator using simple randomization with an equal allocation ratio. During randomization, the proportional allocation of each clinical stratum was equalized in both groups." Appropriate method.
Allocation concealment (selection bias)	High risk	Not reported. Noted more comorbidity, obesity, smoking in HCQ group (although not statistically significant) – this group may have had more risk for more severe disease. Bias in favour of control.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Low for death. High for length of admission and time to clinical improvement. No blinding: open-label. Unlikely to influence mortality, but could affect length of admission (clinician's decision on this, if a clinical vs protocol/virological decision) and time to clinical improvement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low for death. High for length of admission and time to clinical improvement. No blinding: open-label. Unlikely to influence mortality, but could affect length of admission and time to clinical improvement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No report of loss to follow-up, or missing data. No plan reported for imputation for missing data. No trial flow diagram.
Selective reporting (reporting bias)	High risk	No detailed protocol provided with the report or found online. 1 outcome (virological response) in registry record not reported in trial report. Other outcomes (e.g. time to clinical improvement) reported in trial report but not registry record.

Boulware 2020

Study characteristics	
Methods	Double-blind RCT comparing outcomes in people receiving HCQ as post-exposure prophylaxis vs those receiving placebo. Follow-up involved sending participants surveys by email – completed online on REDCap: at days 1, 5, 10, and 14; then at 4 to 6 weeks. "Participants who did not respond to follow-up surveys received text messages, e-mails, telephone calls, or a combination of these to ascertain their outcomes. When these methods were unsuccessful, the emergency contact provided by the enrollee was contacted to determine the participant's illness and vital status. When all communication methods were exhausted, Internet searches for obituaries were performed to ascertain vital status."
Participants	Setting: community; recruitment via social media. Number of participants: 821 total: 414 allocated to HCQ; 407 allocated to placebo. Inclusion criteria: "known exposure (by participant report) to a person with laboratory-confirmed COVID-19, whether as a household contact, a health care worker, or a person with other occupational exposures". Recruited < 3 days after presumptive-case exposure (17 March); then updated to < 4 days after confirmed-case exposure (23 March). Exposure was defined as < 6-feet distance, for > 10 minutes, without full personal protection. This was subdivided into high risk (no mask and no eye protection) and moderate risk (wearing a mask but no eye protection).

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Boulware 2020 *(Continued)*

	Exclusion criteria: < 18 years old; hospitalized; symptoms of COVID-19; PCR positive for SARS-CoV-2; others listed in appendix, such as certain medical conditions and co-medications. Age: HCQ arm: median 41 years (interquartile range: 33 to 51); placebo arm: median 40 years (interquartile range: 32 to 50). Sex: HCQ arm female:male 218:196; placebo arm female:male 206:201. Types of participant: HCQ arm: 275 healthcare workers, 125 household contacts, 14 exposure not reported; placebo arm: 270 healthcare workers, 120 household contacts, 17 exposure not reported. Definition of development of COVID-19: confirmed: by PCR; probable: "presence of cough, shortness of breath, or difficulty breathing, or the presence of two or more symptoms of fever, chills, rigors, myalgia, headache, sore throat, and new olfactory and taste disorders"; possible: "presence of one or more compatible symptoms, which could include diarrhoea". Probable and possible were defined by 4 blinded physicians. Comorbidities: HCQ arm (total 414) vs placebo arm (total 407): 4 vs 2 cardiac disease; 51 vs 48 hypertension; 12 vs 16 diabetes mellitus; 1 vs 0 HIV; 2 vs 2 other immunosuppression; 31 vs 31 asthma; 3 vs 0 other chronic lung disease; 1 vs 2 cancer/malignancy; 0 vs 3 chronic kidney disease.
Interventions	HCQ "800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) daily for 4 more days for a total course of 5 days (19 tablets total)." Oral; could split doses if developed gastrointestinal upset. Placebo = folate tablets; taken as per the HCQ schedule.
Outcomes	Primary – at day 14 from enrolment: development of confirmed or probable COVID-19 (see Participants for definitions). Secondary: hospitalization for COVID-19 or death; PCR-confirmed SARS-CoV-2 infection; COVID-19 symptoms; discontinuation of the trial intervention - from any cause; "severity of symptoms (if any) at days 5 and 14 according to a visual analogue scale (scores ranged from 0 [no symptoms] to 10 [severe symptoms])." Adverse events: directed questioning for common side effects along with open-ended free text. The authors stated regarding losses to follow-up: Of the 821 participants who underwent randomization, 96 did not complete the day 14 follow-up survey, of whom 8 formally withdrew from the trial (4 in each group). Investigators confirmed the vital status and lack of infection in 19 participants (10 in the hydroxychloroquine group and 9 in the control group); 17 completed some follow-up surveys without symptoms before being lost to follow-up (13 in the hydroxychloroquine group and 4 in the control group). A total of 52 participants never completed any surveys after enrolment and did not respond to investigators e-mails, text messages, or telephone calls (23 in the hydroxychloroquine group and 29 in the control group).
Notes	Dates of recruitment: 17 March to 6 May 2020 Sponsors/funders: "Supported by David Baszucki and Jan Ellison Baszucki, the Alliance of Minnesota Chinese Organizations, the Minnesota Chinese Chamber of Commerce, and the University of Minnesota."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted-block sequence – variably sized blocks, stratified by country
Allocation concealment (selection bias)	Low risk	"Randomization will be recorded on an electronic log by the pharmacy. Study investigators and subjects will be blinded."

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Boulware 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded participants and investigators – pharmacies that packaged drug were separate and drug was sent by FedEx. A minority of participants knew what their allocation was for HCQ and placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors not in pharmacies, and blinded from allocation sequence. Outcomes assessed by online survey, then analysed by outcome assessors – so reduced opportunity for outcome data collection to be biased.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasonably low attrition (10% to 11%); similar between groups; similar characteristics of those lost to follow-up in each group; sensitivity analysis including these as having events found no difference in primary outcome.
Selective reporting (reporting bias)	Unclear risk	There was a change in the primary outcome, from confirmed COVID-19, to include probable/possible cases. Confirmed also reported separately. Justified by lack of access to confirmatory testing.

Cavalcanti 2020

Study characteristics	
Methods	3-arm RCT comparing HCQ with HCQ plus azithromycin and a control group receiving standard care for treatment of COVID-19. Participants, clinicians, and outcome assessors in hospital were not blinded, but researchers continuing post-discharge follow-up were. No placebo was used. Follow up to 15 days post-randomization.
Participants	Setting: 55 hospitals in Brazil, mostly Southeast Brazil. Number of participants: HCQ+AZ 217 (172 in modified ITT); HCQ alone 221 (159 in modified ITT); no HCQ/AZ 227 (173 in modified ITT). Inclusion criteria: Hospitalized patients aged 18 or older with suspected or confirmed COVID-19 with symptom onset fewer that 14 days. Confirmed COVID-19 was defined as RT-PCR positive from nose and throat swabs. Suspected COVID-19 was defined according to the Brazilian Ministry of Health criteria: patients with fever and at least 1 respiratory sign or symptom (cough, shortness of breath, nasal congestion, sore throat, peripheral oxygen saturation < 95%, cyanosis, dyspnoea); those from an endemic region or travelling from an endemic region in the last 14 days; or those in contact in the last 14 days with someone with a suspected or confirmed COVID-19 diagnosis. Exclusion criteria: 1. Need for oxygen supplementation > 4 L/min via nasal cannula or ≥ 40% via Venturi mask. 2. Need for oxygen supplementation via high-flow nasal cannula. 3. Need for non-invasive ventilation. 4. Need for invasive mechanical ventilation. 5. Previous use of chloroquine, hydroxychloroquine, azithromycin, or any other macrolide for more than 24 hours before enrolment. 6. History of severe ventricular cardiac arrhythmia or electrocardiogram with QTc ≥ 480 ms. 7. History of liver cirrhosis. 8. Chronic renal failure (eGFR < 30 mL/min/1.73 m^2). 9. Known retinopathy or macular degeneration. 10. History of pancreatitis. 11. Less than 18 years of age. 12. Known allergy to chloroquine or hydroxychloroquine.

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Cavalcanti 2020 *(Continued)*

	13.Known allergy to azithromycin. 14.Pregnancy or breastfeeding. Age (years): HCQ+AZ: Mean 49.5 ± 13.4 SD; HCQ alone: Mean 50.1 ± 13.5 SD; no HCQ/AZ: Mean 50.5 ± 14.7 SD. Sex: HCQ+AZ: female:male 94:123; HCQ alone: female:male 79:142; no HCQ/AZ: female:male 106:123. Clinical presentation: not reported. COVID-19 disease severity at presentation: Asymptomatic and severe patients excluded; HCQ+AZ: mild: 125/217 (58%); moderate 92/217 (42%); HCQ alone: mild 132/221 (60%); moderate 89/221 (40%); no HCQ/AZ: mild 130/227 (57%); moderate 97/227 (43%). Time from symptom onset to randomization: HCQ+AZ: median 7 [IQR 5-9] days; HCQ alone: median 7 [IQR 5-8] days; no HCQ/AZ: median 7 [IQR 4-9] days. Comorbidities: 1. Heart failure: HCQ+AZ 4/217; HCQ alone 3/221; No HCQ/AZ 3/227 2. Hypertension: HCQ+AZ 81/217; HCQ alone 94/221; No HCQ 83/227 3. Diabetes mellitus: HCQ+AZ 40/217; HCQ alone 47/221; No HCQ/AZ 40/227 4. HIV/AIDS: HCQ+AZ 1/217; HCQ alone 0/221; No HCQ/AZ 3/227 5. Chronic airways disease (asthma or COPD): HCQ+AZ 20/217; HCQ alone 13/221; No HCQ/AZ 19/227 6. Smoking history: HCQ+AZ 17/217; HCQ alone 12/221; No HCQ/AZ 15/227 7. Obesity: HCQ+AZ 29/217; HCQ alone 37/221; No HCQ/AZ 37/227 8. Cancer: HCQ+AZ 7/217; HCQ alone 4/221; No HCQ/AZ 8/227 9. Chronic renal disease: HCQ+AZ 2/217; HCQ alone 1/221; No HCQ/AZ 2/227 Place of care: inpatients in hospital.
Interventions	HCQ group received hydroxychloroquine 400 mg orally twice daily for 7 days. HCQ plus azithromycin group received hydroxychloroquine 400 mg orally twice daily and azithromycin 500 mg orally once daily for 7 days. Control group received standard care.
Outcomes	Primary outcome: clinical status on a 7-point ordinal scale at day 15. 1 - indicated not hospitalized with no limitations on activities; 2 - not hospitalized but with limitations on activities; 3 - hospitalized and not receiving supplemental oxygen; 4 - hospitalized and receiving supplemental oxygen; 5 - hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or non-invasive ventilation; 6 - hospitalized and receiving mechanical ventilation; 7 - death. Secondary outcomes: • Clinical status at 7 days on 6-point ordinal scale (points 1 and 2 above combined). • Receipt of oxygen via high-flow nasal cannula or non-invasive ventilation. • Indication for intubation within 15 days. • Duration of hospital stay. • In-hospital death.

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Cavalcanti 2020 *(Continued)*

- Thromboembolic complications.
- Acute kidney injury.
- Number of days alive and free from respiratory support up to 15 days.

Notes	Dates of recruitment: first patient randomized 29 March 2020; the last patient underwent randomization on 17 May 2020; follow-up was completed on 2 June 2020. Funding and sponsorship: the trial was funded by the hospitals and research institutes participating in Coalition Covid-19 Brazil. EMS Pharma provided additional funding and logistic support for the trial and also donated and supplied the trial drugs. EMS Pharma had no role in the conduct of the trial, the analysis, or the decision to submit the manuscript for publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed in blocks of six and was stratified according to the use or nonuse of supplemental oxygen at the time of randomization. Randomization was performed centrally by means of an electronic case-report form system (RedCap) as described in the Supplementary Appendix." However, 1 instance of "duplicate randomization" is reported, without further explanation.
Allocation concealment (selection bias)	Low risk	"The trial statistician, not involved with patient enrolment or care, generated the randomization table in R software (R Core Team, 2019) and implemented in the RedCap. The study treatment was revealed to investigators only after patients were registered in the RedCap, ensuring proper concealment of the allocation sequence."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear for primary outcome Low for mortality Unclear for safety outcomes No blinding of participants and personnel. Some participants in the control group were given study drugs (12%), and decisions to discharge and institute respiratory support may have been influenced. The effect of this is unclear for all outcomes except mortality.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low for primary outcome Low for mortality Unclear for safety outcomes Assessors of the primary outcome were blinded, and the ordinal scale measurement was sufficiently objective. Secondary outcomes were also measured in a predefined objective way, which would minimize risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition for all outcomes, so lack of imputation for missing values was not a problem.
Selective reporting (reporting bias)	High risk	Changes in outcome and analysis approach described, but they occurred after start of participant recruitment, and without adequate explanation provided. However, sensitivity analysis, ITT approach, and mITT approach do not show a difference in results.

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Chen 2020a

Study characteristics	
Methods	RCT investigating treatment with HCQ vs standard care without HCQ. No blinding or placebo used. Follow-up: “On the 0th, 3rd, 5th and 7th day of enrolment, the subjects' vital signs, clinical symptoms, laboratory test results, and adverse events recorded. The study was followed up for 2 weeks.” It was implied that all of this occurred in hospital.
Participants	Setting: Shanghai Public Health Clinical Center, Shanghai, China. Number of participants: 30 randomized: 15 assigned to receive HCQ ("HCQ arm"); 15 assigned to standard care without HCQ ("standard care arm"). Inclusion criteria: 1. Age ≥ 18 years old 2. Confirmed COVID-19 according to Chinese national guidelines 3. Signed informed consent Exclusion criteria: 1. Allergy to chloroquine/hydroxychloroquine 2. Pregnancy 3. "Combined heart, lung, kidney, brain, blood, etc. - patients with serious diseases of important organs and dysfunction" 4. "Retinal diseases, hearing loss or hearing loss" 5. "Serious patients with neurological or psychiatric disorders" 6. "Researchers believe that they cannot complete the study as required or are not suitable to participate in the research" Age: HCQ arm: mean 50.5 ± 3.8; standard care arm: mean 46.7 ± 3.6. Sex: HCQ arm: female:male 6:9; standard care arm: female:male 3:12. Method of diagnosis: not reported; inferred that all had positive RT-PCR on “pharyngeal swabs, sputum, or lower respiratory tract secretions”, as clearance of SARS-CoV-2 from these was the primary outcome. Clinical presentation: all 30 participants assumed to have lower respiratory tract disease, due to abnormality on CT chest scan being present for all at baseline. COVID-19 disease severity at presentation: all 30 participants assumed to have moderate severity, due to abnormality on CT chest scan prompting classification as moderate severity in the Chinese diagnosis and treatment guidelines, and exclusion of individuals with severe disease. Time from symptom onset to enrolment (mean ± standard deviation): HCQ arm: 6.6 ± 3.9 days; standard care arm: 5.9 ± 4.1 days. Comorbidities: hypertension in 5/15 HCQ arm participants vs 3/15 standard care; diabetes mellitus in 1/15 HCQ arm participants vs 1/15 standard care. Place of care: all participants were cared for in hospital.
Interventions	HCQ arm: HCQ 400 mg once daily for 5 days. Additionally, all had nebulized interferon alpha; 12/15 had umifenovir (Arbidol). Standard care arm: no HCQ; all had nebulized interferon alpha; 10/15 had umifenovir (Arbidol). 2 participants received lopinavir/ritonavir, but it is not reported which group they were in.

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Chen 2020a *(Continued)*

Outcomes	Primary: "virological clearance of pharyngeal swabs, sputum, or lower respiratory tract secretions on day 7 or death" Secondary: "occurrence of serious adverse drug events within 2 weeks or the subject's condition turned severe and critical"
Notes	Dates of recruitment: 6 February to 25 February 2020 Sponsors/funders: "Shanghai Science and Technology Commission (20431900103); First-class university and first-class discipline construction project of Fudan University (IDF162005) Zhejiang University New Coronavirus Pneumonia Emergency Scientific Research Project (2020XGZX030); Shanghai Public Health Clinical Center New Coronavirus '2019-nCoV' scientific research project special project in the hospital (2020YJKY01); Shanghai key specialty infectious disease project (shslczdzk01102); Haishi 'Medical Garden New Star' Medical Talent Project (2019-72)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No details reported, but an identical group size with such a small number of participants is suspicious for poorly performing randomization process.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but performance bias unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but unlikely to have influenced outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data are complete on the primary outcome.
Selective reporting (reporting bias)	High risk	The publicly available protocol (clinicaltrials.gov/ct2/show/NCT04261517) reports different outcome measures, except for virological clearance at 7 days, without providing justification.

Chen 2020b

Study characteristics

Methods	RCT comparing outcomes in participants receiving HCQ vs those not receiving HCQ. Reported to be double-blind, but no placebo given, and no details reported of methods used to blind participants and investigators from knowledge of treatment allocation. Follow-up: clinical assessment of body temperature and cough 3 times a day, until 6 days from enrolment, "or severe adverse reactions appeared".
Participants	Setting: Renmin Hospital of Wuhan University, Wuhan, Hubei province, China (tertiary referral hospital).

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Chen 2020b *(Continued)*

	Number of participants: 62 total: 31 received HCQ ("HCQ arm"); 31 did not receive HCQ ("standard care arm"). Inclusion criteria: "1. Age ≥ 18 years; 2. Laboratory (RT-PCR) positive of SARS-CoV-2; 3. Chest CT with pneumonia; 4. SaO2/SPO2 ratio > 93% or PaO2/FiO2 ratio > 300 mmHg under the condition in the hospital room (mild illness); 5. Willing to receive a random assignment to any designated treatment group and not participating in another study at the same time." Exclusion criteria: "1. Severe and critical illness patients or participating in the trial does not meet the patient's maximum benefit or does not meet any criteria for safe follow-up in the protocol after a doctor's evaluation; 2. Retinopathy and other retinal diseases; 3. Conduction block and other arrhythmias; 4. Severe liver disease (e.g., Child-Pugh score ≥ C or AST> twice the upper limit); 5. Pregnant or breastfeeding; 6. Severe renal failure [eGFR ≤ 30 mL/min/1.73m2] or receiving renal replacement therapy; 7. Possibility of being transferred to another hospital within 72 hours; 8. Received any trial treatment for COVID-19 within 30 days before this research." Age: HCQ arm: mean 44.1 (SD 16.1) years; standard care arm: mean 45.2 (SD 14.7) years. Sex: HCQ arm: female:male 17:14; standard care arm: female:male 16:15. Method of diagnosis: positive PCR for SARS-CoV-2; specimen type not reported. Clinical presentation: all had lower respiratory tract disease, as evidenced by pneumonia on chest CT scan. COVID-19 disease severity at presentation: all mild. Time from symptom onset to enrolment: not reported. Comorbidities: not reported. Place of care: inpatients in hospital.
Interventions	HCQ arm: HCQ 200 mg orally twice daily for 5 days. Standard care arm: no HCQ. "All received the standard treatment (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids)"; no further details reported.
Outcomes	Time to clinical recovery: "defined as the return of body temperature and cough relief, maintained for more than 72 h. Normalization and mitigation criteria included the following: a. Body temperature ≤36.6 °C on the surface, ≤ 37.2 °C under the armpit and mouth or ≤ 37.8 °C in the rectum and tympanic membrane; b. Cough from patients' reports, slight or no cough was in the asymptomatic range." Measured in 39 patients with fever at enrolment and 37 patients with cough at enrolment. "For radiological changes, the chest CT results in one day before (Day 0) and one day after (Day 6) the study for evaluation. Pulmonary recovery is defined as three levels: exacerbated, unchanged, and improved, moderately improved when less than 50 % of pneumonia were absorbed, and more than 50 % means significantly improved." Adverse events (all patients).
Notes	Dates of recruitment: 4 February to 28 February 2020 Sponsors/funders: "Funding: This study was supported by the Epidemiological Study of COVID-19 Pneumonia to Science and Technology Department of Hubei Province (2020FCA005)." This study was available as a preprint ahead of publication at the time of completion of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Random sequence generation (selection bias)	Low risk	"Randomization was performed through a computer-generated list stratified by site." Note only 1 hospital site is reported.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported as double-blinded: "Neither the research performers nor the patients were aware of the treatment assignments." However, oral tablets given, and no placebo given, and no methods describing blinding of the prescribing clinician, nor what the patients were told about the tablets they were given.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Due to the nature of the primary outcome (time to clinical improvement), outcome assessment could have been influenced by lack of blinding, therefore with no details about blinding methods and no placebo, judged as high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all participants.
Selective reporting (reporting bias)	High risk	Outcomes listed on the trial registry record differ from the reported outcomes, with no predefined methods for the primary outcome reported.

Chen 2020c

Study characteristics	
Methods	Open-label RCT comparing HCQ with standard care without HCQ. No placebo used. Followed up to 14 days.
Participants	Setting: 11 public hospitals in northern, central, and southern Taiwan. Inclusion criteria: "Enrolled patients were aged 20–79 y and confirmed positive for SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (rRT-PCR)." Exclusion criteria: "Participants presenting with severe illness were excluded from this study. The following patients were excluded from the trial: (a) documented history of hypersensitivity to quinine derivatives; (b) retinal disease; (c) hearing loss; (d) severe neurological or mental illness; (e) pancreatitis; (f) lung disease; (g) liver disease (ALT/AST > 3× the normal upper limit); (h) kidney disease (eGFR < 30 mL/min/1.73 m2 according to MDRD or CKD-EPI); (i) haematological disease; (j) ECG screening with long QT syndrome or QTcF interval > 450 msec for males and > 470 msec for females at screening; (k) known HIV infection; (l) active hepatitis B or C without concurrent treatment (positive for hepatitis B [HBsAg and HBeAg] or hepatitis C ribonucleic acid [RNA] titer > 800,000 IU/mL); (m) G6PD; (n) psychiatric disorders and alcohol/substance dependence/abuse that may jeopardize patient safety; and (o) pregnant or breast-feeding women... Patients who had undetected virus within 2-days of hospitalization were excluded." Age: HCQ arm: mean 33 (SD 12) years; standard care arm: mean 32.8 (SD 8.3) years. Sex: HCQ arm female:male 10:11; standard care arm female:male 4:8. Method of diagnosis: positive PCR for SARS-CoV-2; specimen type not reported. Clinical presentation: not reported specifically, but at least 2/21 in the HCQ arm and 2/12 in the standard care arm had some infiltration of the lungs on imaging of the chest.

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Chen 2020c *(Continued)*

	COVID-19 disease severity at presentation: HCQ arm: 19/21 mild, 2/21 moderate; standard care arm: 10/12 mild, 2/12 moderate. Time from symptom onset to enrolment: not reported. Comorbidities: not reported. Place of care: all hospitalized.
Interventions	HCQ: 400 mg orally twice daily on day 1, then 200 mg twice daily on days 2 to 7. Standard care: all participants with moderate disease had "(1) ceftriaxone 2 g daily for 7 days +/- azithromycin 500 mg on day 1 and 250 mg on days 2–5; or (2) levofloxacin 750 mg daily for 5 d; or (3) levofloxacin 500 mg daily; or (4) moxifloxacin 400 mg daily for 7–14 days for subjects allergic to ceftriaxone or azithromycin or according to physician discretion."
Outcomes	Primary: "time to negative rRT-PCR assessments from randomization up to 14 days." Secondary: • negative PCR for SARS-CoV-2 on hospital day 14 • "resolution of clinical symptoms (time to clinical recovery)" • discharge by day 14 • mortality "HCQ safety and tolerability were also evaluated."
Notes	Dates of recruitment: 1 April to 31 May 2020. Sponsors/funders: "The authors thank the Hospital and Social Welfare Organizations Administration Commission, Ministry of Health and Welfare for their research grant. This funding source played no role in study design or conduction, data collection, analysis or interpretation, writing of the manuscript, or decision to submit it for publication. The authors also thank Taiwan Biotech Co. Ltd. for their donation of investigational products, the National Health Research Institutes, Taiwan Centers for Disease Control, Taiwan Food and Drug Administration, Center for Drug Evaluation, Taiwan for their technical assistance" A retrospective study was also conducted, reviewing records of patients preceding the trial. Its results are not extracted here.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned by an interactive web response system in a 2:1 ratio to receive either HCQ plus standard of care (SOC) or SOC alone. They were stratified by mild or moderate illnesses within 4 days of diagnosis."
Allocation concealment (selection bias)	Unclear risk	No allocation sequence concealment reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Low for time to negative PCR, negative PCR on day 14, and mortality. High for discharge by day 14 and adverse events. Unclear for time to clinical recovery. No blinding. Unlikely effect on time to negative PCR, negative PCR on day 14, or mortality. High risk of bias for discharge and adverse events. Unclear risk of bias for time to clinical recovery – no methods reported for how this was determined.

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Chen 2020c *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low for time to negative PCR, negative PCR on day 14, and mortality. High for discharge by day 14, time to clinical recovery and adverse events. No blinding. Unlikely effect on time to negative PCR, negative PCR on day 14, or mortality. High risk of bias for discharge by day 14, adverse events, and time to clinical recovery.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition of ~10% (3/33) before first dose of HCQ (1/21 HCQ arm; 2/12 standard of care arm), with no reason or characteristics reported. Imputation of PCR results not available as negative results, with no sensitivity analysis, nor reporting of how much missing data there were for each outcome. With such a small sample size, effect may be influenced by this degree of missing data.
Selective reporting (reporting bias)	High risk	No trial protocol is available. Clinical efficacy outcomes were not reported in the trial registry entry (clinicaltrials.gov/ct2/show/record/NCT04384380); only virological outcomes (time to negative PCR = primary) and adverse events listed.

Davoodi 2020

Study characteristics	
Methods	Open-label RCT comparing HCQ with febuxostat. No placebo. Followed up to 14 days.
Participants	Setting: outpatients at Mostafavian Fever Clinic in Sari, Iran. Number of participants: 54 total: 25 received HCQ; 29 received febuxostat. Inclusion criteria: "1; chest CT finding compatible with COVID-19 infection along with other symptoms of coronavirus infection. Bilateral and peripheral ground-glass and consolidative pulmonary opacities were the hallmarks of CT findings. 2; any symptoms of respiratory tract involvement including cough, dyspnoea or tachypnoea along with a history of contact with a known case of COVID-19. 3; creatinine clearance greater than 60 mL/min." Exclusion criteria: "1; Suspicious patients for COVID-19 pneumonia who had severe underlying diseases such as cardiovascular, lung and kidney diseases, 2; patients with severe pneumonia needing hospitalisation, 3; patient who were unable to take oral medications and 4; concurrent use of azathioprine, didanosine, mercaptopurine or pegloticase (due to drug interaction with febuxostat)." Age: HCQ arm: mean 57.3 (standard error 2.2) years; febuxostat arm: mean 58 (standard error 1.47) years. Sex: HCQ arm female:male 9:16; febuxostat arm female:male 13:16. Method of diagnosis: based on CT scan and symptoms, as in inclusion criteria above. Clinical presentation: not specifically reported, but all had some lung abnormalities on CT chest scan. COVID-19 disease severity at presentation: presumed to all have moderate disease based on WHO classification: all had pneumonia on CT. Time from symptom onset to enrolment: not reported. Comorbidities: 7/25 in the HCQ arm and 8/29 in the febuxostat arm had diabetes mellitus; 1/25 in the HCQ arm and 0/29 in the febuxostat arm had underlying lung disease. Place of care: ambulatory care.

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Davoodi 2020 *(Continued)*

Interventions	HCQ: 200 mg orally twice daily for 5 days. Febuxostat: 80 mg orally once daily for 5 days. "All patients were taken acetaminophen [paracetamol] 325 mg, as needed, for controlling the fever." No other co-interventions reported.
Outcomes	Primary: need for hospitalization. Secondary: • "clinical improvements (eg, resolution of fever, cough and dyspnoea)"; and • "improvement of CT findings" at day 14 after initiation of the treatment.
Notes	Dates of recruitment: 16 March to 10 April 2020. Sponsors/funders: "This study was supported by a grant from Mazandaran University of Medical Science, Sari, Iran (ID#7294)." Febuxostat was the intervention drug of interest for this trial; HCQ was an active comparator.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description beyond "randomised using the balance block method".
Allocation concealment (selection bias)	Low risk	"The patient receives the medication (intervention or comparison) in sealed envelopes that are coded. The coding is done by a project colleague and the physician, assessor and patient are blind."
Blinding of participants and personnel (performance bias) All outcomes	High risk	High for hospitalization (primary) and clinical improvement Low for improvement of CT scan Reported as open-label, but also states: "Both patients and physician did not know the contents of tables [tablets]." No measures for blinding described, and the interventions had different frequencies of administration. If assumed to be open-label, hospitalization and clinical improvement would be at high risk of performance bias. Improvement of CT scan findings would be at low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low for hospitalization (primary) and improvement of CT scan High for clinical improvement Reported as open-label, but also states: "Both patients and physician did not know the contents of tables [tablets]." No measures for blinding described, and the interventions had different frequencies of administration. If assumed to be open-label, clinical improvement would be at high risk of detection bias. Hospitalization and improvement of CT scan findings would be at low risk of detection bias.

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Davoodi 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	No outcome data used for 5/30 participants randomized to HCQ arm and 1/30 to febuxostat arm. Reasons provided, but neither baseline characteristics nor outcomes reported, and no imputation performed for these participants. With small total trial numbers, and possibility of some participants not having remained in trial due to poor outcomes, we judged this domain as high risk.
Selective reporting (reporting bias)	High risk	In registry record, outcomes: CT scan findings (primary), fever, lymphocyte count, CRP. In report: hospitalization (primary), "clinical improvements (eg, resolution of fever, cough and dyspnoea)", "improvement of CT findings". No reason given for change in outcomes, especially primary outcome.

Horby 2020

Study characteristics	
Methods	Adaptive factorial design RCT (RECOVERY) comparing a HCQ with standard of care (SOC) in patients hospitalized with COVID-19. The RECOVERY trial evaluated several treatments, of which only HCQ was relevant for this review. Centralized web-based randomization was done. There was no blinding of participants or personnel. Follow-up: Data were collected at time of death, discharge, or 28 days after randomization. Data were available for 98% of participants for the 28-day follow-up.
Participants	Setting: UK National Health Service (NHS) hospitals - secondary and tertiary facilities (176 in total) Number of participants: 4674 total: 1542 received HCQ; 3132 received SOC Inclusion criteria: hospitalized AND SARS-CoV-2 infection (clinically suspected or laboratory confirmed) AND without a medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial. Exclusion criteria: only those 18 years and above were eligible, until 9 May after which children were included. Exclusions included those with known prolonged electrocardiograph QTc interval. Co-administration with medications that prolong the QT interval was not an absolute contraindication, but attending clinicians were advised to check the QT interval by performing an electrocardiogram. Age: HCQ arm: mean 65.2 (SD 15.2) years; standard care arm: mean 65.4 (SD 15.4) years. Sex: HCQ arm: female:male 600:961; standard care arm: female:male 1181:1974. Method of diagnosis: clinically suspected or laboratory confirmed were included. Clinical suspicion was suspected when a patient presented with (i) typical symptoms (e.g. influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); and (ii) compatible chest X-ray findings (consolidation or ground-glass shadowing); and (iii) alternative causes have been considered unlikely or excluded (e.g. heart failure, influenza). Method of laboratory testing not specifically described, but antibody testing not used in most UK hospitals. HCQ: positive "SARS-COV-2 test": 1393 (89%); negative 153 (10%); unknown 15 (1%). SOC: positive "SARS-COV-2 test": 2841 (90%); negative 291 (9%); unknown 23 (1%). A small number of children (age < 18 years old) presented with atypical features, including a hyperinflammatory state and evidence of single or multi-organ dysfunction. Some did not have significant lung involvement. Clinical presentation: not specifically reported, but 77% (HCQ) vs 76% (SOC) were receiving oxygen or invasive ventilation at enrolment.

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Horby 2020 *(Continued)*

	COVID-19 disease severity at presentation: HCQ: no oxygen received 362 (23%); received oxygen: 938 (60%); invasive ventilation 261 (17%). SOC: no oxygen received 750 (24%); received oxygen: 1873 (59%); invasive ventilation 532 (17%). Time from symptom onset to enrolment: HCQ: median 9 days (IQR 5 to 14); SOC: median 9 days (IQR 5 to 13); this is presumed to be time from symptom onset to randomization, not to hospital presentation. Comorbidities: 1. cardiac disease (such as coronary artery disease or heart failure): HCQ: 422 (27%) and SOC: 789 (25%); 2. diabetes mellitus: HCQ: 427 (27%) and SOC: 856 (27%); 3. HIV: HCQ: 8 and SOC: 13; 4. chronic airways disease (asthma, COPD): HCQ: 334 (21%) and SOC: 712 (23%); 5. severe liver disease: HCQ: 18 (1%) and SOC: 46 (1%); 6. severe kidney impairment: HCQ: 111 (7%) and SOC: 261 (8%); 7. tuberculosis: HCQ: 4 and SOC: 9. Place of care: inpatients in hospital.
Interventions	Oral formulation of HCQ given at dosage of 800 mg at 0 and 6 hours, then 400 mg at 12 hours from first dose and every 12 hourly for 10 days.
Outcomes	Primary outcome: all-cause mortality at 28 days after randomization. Secondary outcomes: • duration of hospital stay • need for (and duration of) ventilation • composite endpoint of death or need for mechanical ventilation/ECMO • need for renal replacement therapy • new major cardiac arrhythmias Regarding major new cardiac arrhythmia, data were collected for 698 (44.7%) patients in the HCQ arm and 1357 (43.0%) in the SOC arm; supraventricular tachycardia was observed in 6.9% HCQ participants vs 5.9% SOC; ventricular tachycardia or fibrillation in 0.9% HCQ vs 0.7% SOC; and atrioventricular block requiring intervention in 0.1% HCQ vs 0.1% SOC. No other data regarding adverse events provided.
Notes	Dates of recruitment: 25 March to 5 June 2020 Sponsors/funders: Nuffield Department of Population Health at University of Oxford. The RECOVERY trial is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) (Grant reference: MC_PC_19056) and by core funding provided by NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Department for International Development, Health Data Research UK, the Medical Research Council Population Health Research Unit, the NIHR Health Protection Unit in Emerging and Zoonotic Infections, and NIHR Clinical Trials Unit Support Funding. This study was available as a preprint ahead of publication at the time of completion of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"central web-based randomisation service (without stratification or minimisation)"
Allocation concealment (selection bias)	Low risk	Handled centrally, so unlikely.

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Horby 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding used. Clinicians could decide eligibility for each arm of the trial on an individual basis, which could lead to systematic bias in comparability of the 2 groups; however, due to the comparison for each intervention being with controls who were eligible for that intervention, and this is pre-randomization, it is unlikely to lead to a high risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low for death and invasive ventilation Unclear for discharge Unlikely to influence mortality or need for invasive ventilation, but unclear effect on discharge decision.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up data available for 98% of participants.
Selective reporting (reporting bias)	Low risk	Low for all outcomes, except unclear for time to discharge and adverse events. Reported outcomes decided a priori. Insufficient detail of time to discharge and adverse events. However, this is a preprint, so further details may become available.

Huang 2020

Study characteristics	
Methods	RCT comparing outcomes in participants receiving CQ with those receiving lopinavir/ritonavir (LPV/r). Blinding not reported. Participants had daily clinical data collection and nasopharyngeal swab PCR for SARS-CoV-2. They had follow-up CT chest scans (unclear frequency). Outcomes were reported to be measured up to 14 days.
Participants	Setting: Fifth Affiliated Hospital of Sun Yat-sen University in Zhuhai, China. Number of participants: 22 total: 10 received CQ; 12 received LPV/r. Inclusion criteria: age ≥ 18 years old; hospitalized; positive PCR for SARS-CoV-2. Exclusion criteria: "1. Pregnant woman patients; 2. Documented allergic history to Chloroquine; 3. Documented history of hematological system diseases; 4. Documented history of chronic liver and kidney diseases; 5. Documented history of cardiac arrhythmia or chronic heart diseases; 6. Documented history of retina or hearing dysfunction; 7. Documented history of mental illnesses; 8. Use of digitalis due to the previous disease." Age: CQ arm: median 41.5 (IQR 33.8 to 50.0) years; LPV/r arm: median 53.0 (IQR 41.8 to 63.5) years. Sex: CQ arm female:male 3:7; LPV/r arm female:male 6:6. Method of diagnosis: positive PCR for SARS-CoV-2; specimen type not reported. Clinical presentation: not reported specifically, but at least 8/10 in the CQ arm and 11/12 in the LPV/r arm had some abnormalities on CT chest scan. COVID-19 disease severity at presentation: CQ arm: 7/10 moderate, 3/10 severe; LPV/r arm: 7/12 moderate, 5/12 severe.

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Huang 2020 *(Continued)*

	Time from symptom onset to enrolment: CQ arm: median 2.5 (IQR 2 to 3.75) days; LPV/r arm: median 6.5 (4.75 to 8.5) days. Comorbidities: 1/10 in the CQ arm and 3/12 in the LPV/r arm had hypertension; 0 in the CQ arm and 1/12 in the LPV/r arm had history of stroke/cerebrovascular disease; 1/10 in the CQ arm and 1/12 in the LPV/r arm had diabetes mellitus; 2/10 in the CQ arm and 0 in the LPV/r had a history of smoking. Place of care: all inpatients in hospital.
Interventions	CQ: 500 mg orally twice daily for 10 days. LPV/r: 400/100 mg orally twice daily for 10 days. No other co-interventions reported.
Outcomes	Primary outcome: time to conversion of SARS-CoV-2 PCR on nasal and pharyngeal swab samples from positive to negative, and proportion (reported as "rate") negative at day 10 and day 14. Secondary outcomes: “rate of hospital discharge at Day 14, clinical recovery at day 10, CT scan improvement at Day 10 and 14, and the frequency of adverse events. The criteria of clinical recovery were: no fever, axilla temperature ≤36.6°C or oral temperature ≤37.2°C or rectal/tympanic temperature ≤37.8°C; respiratory rate ≤24/minute on room air; oxygen saturation >94% on room air; mild or absent of cough (the scale of cough is classified as severe, moderate, mild, absent). The criteria of hospital discharge were: the temperature returned to normal for more than 3 days; the respiratory symptoms improved significantly; the pulmonary imaging showed that the inflammation was obviously absorbed; and the detection of respiratory pathogenic nucleic acid was negative twice in a row (the sampling time is at least 1 day apart). The criteria of CT scan improvement were: exudation or consolidation of the lesion absorbed; the lesion area was gradually narrowed; and there might be residual linear fibrosis.”
Notes	Dates of recruitment: 27 January to 15 February 2020. Sponsors/funders: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No information about method of randomization in trial report, however baseline differences seem significant for duration of symptoms prior to hospital admission, age, baseline severity, and baseline radiographic characteristics. The trial registry protocol states that the study is non-randomized.
Allocation concealment (selection bias)	Unclear risk	No information reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but low risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, and little detail on assessment of outcome, so although possible, it is unlikely that interpretation of the result may have been influenced by knowledge of treatment received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete data for all participants.
Selective reporting (reporting bias)	High risk	Protocol on the trials registry (ChiCTR2000029542) lists different outcomes from protocol in the article supplement.

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Mitjà 2020a

Study characteristics	
Methods	RCT evaluating early treatment of mild COVID-19 with HCQ compared to standard of care (SOC) Follow up: on day 1, patients were visited at home for baseline assessment and participant enrolment. Outbreak field teams verified the selection criteria for eligibility, obtained patients' signed informed consent, assessed specific symptoms associated with COVID-19, and collected relevant epidemiological information from a structured interview. Disease progression, safety, and self-reported treatment compliance were monitored by the Clinical Trials Unit of Hospital Germans Trias Pujol at days 3 and 7 (home visits), 14 and 28 (telephone reviews).
Participants	Setting: participants identified via an electronic registry of the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC) of the National Department of Health, from 3 health administrative regions in Catalonia, Spain. They were managed at home, not hospitalized. Number of participants: 293 total: 136 allocated to HCQ; 157 allocated to standard of care. Inclusion criteria: adult patients aged 18 years or more were eligible if they had mild symptoms of COVID-19 (i.e. fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like illness) for less than 5 days before enrolment, were non-hospitalized, and had a positive PCR test for SARS-CoV-2 in the baseline nasopharyngeal swab. Exclusion criteria: moderate-to-severe COVID-19 disease (e.g. required hospitalization), any condition that might preclude following the study procedures safely (e.g. mental disability), known allergy or hypersensitivity to study drugs, known retinal and severe liver or renal diseases, history of cardiac arrhythmia, known QT prolongation or other diseases that could be exacerbated by study drugs (e.g. psoriasis), active treatment with medications that are contraindicated with study drugs, or known HIV infection. Females who were pregnant (verbally declared or positive pregnancy test) or breastfeeding were also excluded. Age: HCQ arm: mean 41.6 years (SD 12.4); control arm: mean 41.7 years (SD 12.6). Sex: HCQ arm female:male 98:38; standard of care arm female:male 103:54. Types of participant: HCQ arm: 106 healthcare workers, 4 household contacts, 8 nursing home workers, 18 exposure not reported; control arm: 132 healthcare workers, 1 household contacts, 8 nursing home workers, 16 exposure not reported. Severity on presentation: not reported. Time from symptom onset to presentation: all < 5 days by definition; however, note that 4 reported > 5 days symptoms, but duration not reported. Definition of development of COVID-19: positive PCR on nasopharyngeal swab Comorbidities: 1. cardiac disease (such as coronary artery disease or heart failure): HCQ: 20 (14.7%) and SOC: 15 (9.6%); 2. chronic airways disease (asthma, COPD): HCQ: 7 (5%) and SOC: 10 (6%); 3. metabolic disease: HCQ: 9 (6.6%) and SOC: 11 (9%); 4. nervous system disease: HCQ: 19 (14%) and SOC: 21 (13.4%); 5. any co-existing disease: HCQ: 71 (52.2%) and SOC: 85 (54.1%). Care setting: home-based care
Interventions	Intervention group received oral dose of HCQ 800 mg on day 1, followed by 400 mg daily for a further 6 days (total duration of treatment 7 days). Comparator group received standard of care.

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Outcomes	Primary: reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after start of treatment. Secondary: clinical progression measured by a simplified version of the WHO progression scale (1, not hospitalized with or without resumption of normal activities; 2, hospitalized, requiring supplemental oxygen; 3, hospitalized, requiring invasive mechanical ventilation; and 4, death); time from randomization to complete resolution of symptoms within the 28-day follow-up period. Resolution of symptoms was assessed sequentially using a symptoms questionnaire designed to gather information on the type of symptom and last day experienced; complete resolution was considered when no COVID-19-related symptoms were reported. Safety outcomes: adverse events occurring during treatment, serious adverse events, adverse events of special interest (i.e. cardiac), and premature discontinuation of therapy.
Notes	Recruitment: 17 March to 26 May 2020 Sponsor/ funding: mainly supported by the crowdfunding campaign JoEmCorono (www.yomecorono.com/) with the contribution of over 72,000 citizens and corporations. The study also received financial support from Laboratorios Rubió, Laboratorios Gebro Pharma, Zurich Seguros, SYNLAB Barcelona, and Generalitat de Catalunya. Laboratorios Rubió also contributed to the study with the required doses of hydroxychloroquine (Dolquine).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomized (1:1) using a computer-generated random-number list"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Low for viral load reduction at 3 days and 7 days. High for admission to hospital, time to clinical improvement, and adverse events. "Laboratory technicians were unaware of participants' treatment allocation, treatment response, and previous PCR results at all time points." None for participants or investigators (i.e. open-label). Outcomes not affected by lack of blinding: viral load reduction at 3 days and 7 days. Outcomes prone to lack of blinding: admission to hospital and adverse events.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low for viral load reduction at 3 days and 7 days. High for admission to hospital, time to clinical improvement, and adverse events. "Laboratory technicians were unaware of participants' treatment allocation, treatment response, and previous PCR results at all time points." None for participants or investigators (i.e. open-label). Outcomes not affected by lack of blinding: viral load reduction at 3 days and 7 days. Outcomes prone to lack of blinding: admission to hospital and adverse events.

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Mitjà 2020a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Low attrition numbers labelled as "lost to follow up", and 2 further participants withdrew consent without explanation. Denominators very unclear (e.g. 291 vs 293).
Selective reporting (reporting bias)	High risk	Reported to be a secondary trial within this combined postexposure prophylaxis and treatment trial (clinicaltrials.gov/ct2/show/NCT04304053). Not reported clearly in article how many participants were contacts vs index cases. Virological clearance at 3 days reported in ClinicalTrials.gov registry record, but not reported in trial report. Also ClinicalTrials.gov record does not report the ordinal outcome scale used in the report (which is not standard e.g. WHO).
Other bias	High risk	A small number of participants were randomized who were in fact not eligible for the trial; however, these participants were kept in the ITT population, which could have introduced bias.

Mitjà 2020b

Study characteristics	
Methods	Open-label cluster-randomized trial comparing HCQ with standard care when given to individuals with a history of exposure to SARS-CoV-2, for prevention of COVID-19. Follow-up was up to day 28, using in-person visits to the participant's home on days 1 and 14, and telephone interviews on days 3, 7, and 28.
Participants	Setting: community; “screened using the electronic registry of the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC) of the Department of Health. During the COVID-19 outbreak in Catalonia, a public health ordinance required all patients who tested positive for COVID-19 in any of the designated diagnostic laboratories to be notified to the SUVEC.” Number of participants: 2525 total: 1225 allocated to HCQ; 1300 allocated to standard care. (Note that baseline characteristics and efficacy outcomes use a modified ITT population as their denominator: 1116 HCQ; 1198 standard care. Adverse events are reported for all randomized participants: 1225 HCQ; 1300 standard care.) Inclusion criteria: “adult individuals ≥ 18 years of age with a recent history of close contact exposure to a PCR confirmed COVID-19 case (i.e., > 15 minutes within two meters, up to seven days before enrolment) and absence of COVID-19-like symptoms on the two weeks preceding enrolment, as either a healthcare worker, a household contact, a nursing home worker or a nursing home resident.” Exclusion criteria: symptoms or signs of COVID-19 at baseline assessment; “all eligibility criteria are listed in the Supplementary Appendix.” (No appendix was available with the preprint publication.) Age: HCQ arm: mean 48.6 (SD 18.7) years; standard care arm: mean 48.7 (SD 19.3) years. Gender: HCQ arm F:M 813:303; standard care arm F:M 875:323. Types of participant: HCQ arm: 131 (12%) healthcare workers; 302 (27%) household contacts; 550 (49%) nursing home workers; 133 (12%) nursing home residents. Standard care arm: 130 (11%) healthcare workers; 338 (28%) household contacts; 584 (49%) nursing home workers; 160 (13%) nursing home residents. (Note that the denominator for the standard care arm is 1212 rather than 1198.) Definition of development of COVID-19: "confirmed COVID-19 episode, defined as symptomatic illness (at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorder(s), or diarrhoea) and a positive SARS-CoV-2 RT-PCR test"; “SARS-CoV-2 infection, defined as either the RT-PCR detection of SARS-CoV-2 in a nasopharyngeal specimen or the presence of any of the aforementioned symptoms compatible with COVID-19”. Comorbidities:

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Mitjà 2020b *(Continued)*

	1. cardiovascular disease: HCQ: 130 (11.6%) and standard care: 178 (14.9%); 2. respiratory disease: HCQ: 64 (5.7%) and standard care: 47 (3.9%); 3. metabolic disease: HCQ: 99 (8.9%) and standard care: 94 (7.8%); 4. nervous system disease: HCQ: 170 (15.2%) and standard care: 170 (14.2%).
Interventions	HCQ: 800 mg orally on day 1, followed by 400 mg once daily for 6 days. Total 7 days. Standard care: no treatment. Co-interventions not reported.
Outcomes	Primary outcome: "confirmed COVID-19 episode, defined as symptomatic illness (at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorder(s), or diarrhoea) and a positive SARS-CoV-2 RT-PCR test. The primary outcome was assessed in all asymptomatic individuals, irrespective of the PCR result; in a post hoc analysis, we explored the outcome in individuals with positive and negative PCR separately. Time-to-event was defined as the number of days from the date of randomization/exposure to the confirmed date of the onset of symptomatic illness." Secondary efficacy outcomes: • "incidence of SARS-CoV-2 infection, defined as either the RT-PCR detection of SARS-CoV-2 in a nasopharyngeal specimen or the presence of any of the aforementioned symptoms compatible with COVID-19" • "serological positivity (IgM/IgG) of contacts at day 14" Safety outcomes: "frequency and severity of adverse events (AE), serious AE (SAE), and AE of special interest (e.g., cardiac) up to 28 days from treatment start. Causality was assessed by an external panel of pharmacovigilance consultants." (Note that this included death and hospitalization.)
Notes	Recruitment: 17 March to 28 April 2020. Sponsor/funding: "mainly supported by the crowdfunding campaign JoEmCorono (https://www.yomecorono.com/) with the contribution of over 72,000 citizens and corporations. The study also received financial support from Laboratorios Rubió, Gebro Pharma, Zurich Seguros, SYNLAB Barcelona, and Generalitat de Catalunya. Laboratorios Rubió also contributed to the study with the required doses of hydroxychloroquine (Dolquine®)." Note that LR and GP are pharmaceutical companies. No mention of their involvement in the study, or lack thereof.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed remotely by a member of the study team not involved in participants' enrollment." No description of sequence generation method.
Allocation concealment (selection bias)	Unclear risk	"Randomization was performed remotely by a member of the study team not involved in participants' enrollment… The allocation was revealed to participants after providing written consent on day 1 (baseline)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	High for symptomatic confirmed COVID-19 (primary outcome) and adverse events. Low for antibody positivity. Open-label study. Due to symptoms being required to define primary outcome, this would be at high risk of bias due to lack of blinding, as would safe-

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Mitjà 2020b *(Continued)*

		ty outcomes. Antibody positivity at day 14 would not be influenced by knowledge of group allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	High for symptomatic confirmed COVID-19 (primary outcome); composite symptoms without PCR positivity OR PCR-positive asymptomatic COVID-19; and adverse events. Low for antibody positivity and death. No blinding. As above, due to symptoms being required to define primary outcome, this would be at high risk of bias due to lack of blinding, as would safety outcomes. Antibody positivity at day 14/death would not be influenced by knowledge of group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low for efficacy outcomes. Unclear for adverse events. Exclusions from "intention-to-treat (ITT)" (assessed as modified ITT; primary analysis) were < 10%; reasons were reported, and loss to follow-up was < 5%. Numbers seemed to be balanced between the 2 treatment arms. Comparison of characteristics between those included vs excluded not presented in preprint. This applies to all efficacy outcomes. There was no imputation for missing data. The safety sample included all randomized participants, so there was low risk of bias for the outcomes of adverse events and death. < 3% of participants either did not receive HCQ in the HCQ arm or started HCQ in the control arm. However, denominators were unclear: 1197 vs 1225 in the intervention arm.
Selective reporting (reporting bias)	High risk	Both of the outcomes currently specified in the trial registry entry (clinicaltrials.gov/ct2/show/NCT04304053) were included in the report. However, disease in contacts of contacts was also specified and is not reported, with no reason provided.
Other bias	High risk	Additional domains for cluster-RCTs: Recruitment bias: low risk. Appears unlikely, as the rings (clusters) were randomized first, and then the contacts were told their allocation. Baseline imbalance: low risk. No stratified or pair-matched randomization. Baseline characteristics not disaggregated by cluster. But many clusters, so unlikely to lead to baseline imbalance. Loss of clusters: low risk. No clusters lost. Incorrect analysis: low risk. The analysis accounted for clustering. Comparability with individually randomized trials: high risk. Contamination- possible, as this was an open-label study, and people within clusters may encourage differential adherence to intervention. However, reported adherence was > 95%. This intervention would be expected to work best when given to all contacts of a case rather than some being randomized to the intervention and some randomized to no intervention, which would preclude comparability with an individually randomized trial.

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Pan 2020

Study characteristics	
Methods	Adaptive open-label RCT comparing multiple different experimental pharmaceutical interventions vs standard care. Participants in treatment arms were compared only with those eligible for that treatment but that were randomized to standard care. No placebo used. Followed up to hospital discharge.
Participants	Setting: hospitals in 30 countries in all 6 WHO regions; ~60% of participants recruited in Africa/Asia. Number of participants: 1853 total: 947 received HCQ; 906 received standard care. Inclusion criteria: hospitalized adults (> 18 years old) with confirmed COVID-19, receiving any treatment other than the study drugs, with no contraindications to any study drug, and no transfer planned within the subsequent 72 hours. Exclusion criteria: "1. Any of the available study drugs are contra-indicated (e.g. because of patient characteristics, chronic liver or heart disease, or some concurrent medication). 2. Declined to participate in the study." Note that an initial exclusion criterion was pregnancy, but this was removed early in the trial. Age: HCQ arm: 335 participants (< 50 years), 410 (50 to 69 years), 202 (≥ 70 years); standard care arm: 317 participants (< 50 years), 396 (50 to 69 years), 193 (≥ 70 years). Sex: HCQ arm: female:male 373:574; standard care arm: female:male 371:535. Method of diagnosis: not reported, but presumed PCR positivity due to "confirmed" inclusion criterion and WHO-sponsored study. Clinical presentation: not reported. COVID-19 disease severity at presentation: HCQ: 862/947 moderate or severe (of whom 517 were receiving oxygen at randomization), 85 critical; standard care: 824/906 moderate or severe (of whom 483 were receiving oxygen at randomization), 82 critical. Time from symptom onset to enrolment: not reported. Comorbidities: 1. cardiac disease: HCQ: 193/947 and standard care: 194/906; 2. diabetes mellitus: HCQ: 199/947 and standard care: 194/906; 3. chronic lung disease: HCQ: 62/947 and standard care: 66/906; 4. chronic liver disease: HCQ: 15/947 and standard care: 14/947; 5. asthma: HCQ: 41/947 and standard care: 46/906. Place of care: all inpatients in hospital.
Interventions	HCQ: 800 mg orally at 0 and 6 hours, then 400 mg twice daily from 12 hours onwards, for a total of 10 days. Standard care: any drugs that were not part of the study. Co-interventions not reported.
Outcomes	Primary: all-cause death in hospital. Secondary: • Initiation of ventilation (initial on protocol as on 16 October 2020: “Time to first receiving ventilation (or intensive care)”). • Time to discharge from hospital.

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Pan 2020 *(Continued)*

Notes	Dates of recruitment: 22 March to 4 October 2020 for whole report, from which data were extracted; HCQ arm stopped on 18 June 2020. Sponsors/funders: drugs donated by drug companies; WHO and national governments shared sponsorship. Details of the trial results were taken from a preprint publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized computer generated.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but unlikely to lead to performance bias for death.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but unlikely to affect outcome assessment for death.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Near-complete data for death outcome.
Selective reporting (reporting bias)	Unclear risk	Preprint with not all outcomes reported, and 1 changed between protocol and report with no reason provided (www.isrctn.com/ISRCTN83971151, accessed 16 October 2020).

Skipper 2020

Study characteristics

Methods	RCT comparing outcomes in people receiving HCQ for prophylaxis vs those receiving placebo for prevention of COVID-19. Follow-up: participants were sent surveys by email on days 1 (medication start date), 3, 5 (medication stop date), 10, and 14 to assess medication adherence, adverse effects, presence and severity of COVID-19 symptoms, COVID-19 test results, and hospitalization status. If participants were hospitalized, follow-up continued to assess outcomes.
Participants	Setting: community; recruitment via social media campaign. Number of participants: 491 total: 244 allocated to HCQ; 247 allocated to placebo. Inclusion criteria: non-hospitalized adults who were required to have 4 or fewer days of symptoms and either PCR-confirmed SARS-CoV-2 infection or compatible symptoms after a high-risk exposure to a person with PCR-confirmed COVID-19 within the past 14 days. High-risk exposure was defined as an immediate household contact or a close occupational exposure to someone with COVID-19 (e.g. healthcare worker or first responder). Healthcare workers who had COVID-19-compatible symptoms and high-risk exposure but whose contact had PCR results pending were enrolled after symptom review by

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Skipper 2020 *(Continued)*

	an infectious diseases physician. All of these participants met the COVID-19 case definition of the US Council of State and Territorial Epidemiologists. Exclusion criteria: age < 18 years old, current hospitalization, HCQ allergy, retinal disease, known glucose-6 phosphate dehydrogenase deficiency, known chronic kidney disease (stage 4 or 5 or receiving dialysis), known porphyria, weight less than 40 kg, receiving chemotherapy, current use of HCQ, CQ, current use of cardiac arrhythmia medicines of: flecainide; amiodarone; digoxin; procainamide; or sotalol. In Canada, additional exclusions mandated by regulatory authorities were: pregnancy, breastfeeding; severe diarrhoea or vomiting; known cirrhosis with encephalopathy or ascites; known prolonged cardiac QT interval, ventricular arrhythmia, or history of sudden cardiac death; or QT-prolonging medicines. On 20 April 2020, additional US exclusions were added for weight less than 50 kg, structural or ischaemic heart disease, personal or family history of cardiac QT prolongation, and QT-prolonging medications. Concomitant QT-prolonging medications included current use of: antimicrobials: azithromycin clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, or mefloquine; antidepressants: amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, bupropion (Wellbutrin), or venlafaxine; antipsychotic or mood stabilizers: haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone, methadone, sumatriptan, zolmitriptan. The prohibition of azithromycin and other QT-prolonging medicines was at the request of the US Food and Drug Administration as potentially unsafe in an outpatient clinical trial. Age: HCQ arm: median 41 years (IQR 33 to 49); placebo arm: median 39 years (IQR 31 to 50). Sex: HCQ arm female:male 136:123; placebo arm female:male 130:115. Types of participant: HCQ arm: 132 healthcare workers, 59 household contacts; placebo arm: 128 healthcare workers, 82 household contacts. Disease severity: not specifically reported, but it appeared that most were mild at presentation. 47 were asymptomatic in the HCQ arm, and 52 were asymptomatic in the placebo arm. All were < 7 days from onset of symptoms. Definition of development of COVID-19: confirmed SARS-CoV-2 by PCR or meeting the case definition of the US Council of State and Territorial Epidemiologists: in outpatient or telehealth settings at least 2 of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR at least 1 of the following symptoms: cough, shortness of breath, or difficulty breathing OR severe respiratory illness with at least 1 of the following: clinical or radiographic evidence of pneumonia, or acute respiratory distress syndrome (ARDS) AND no alternative more likely diagnosis. Comorbidities: 1. cardiac disease (such as coronary artery disease or heart failure): HCQ: 4 (1.6%) and placebo: 2 (0.8%); 2. hypertension: HCQ: 23 (10.8%) and placebo: 23 (10.9%); 3. diabetes mellitus: HCQ: 8 (3.8%) and placebo: 7 (3.3%); 4. HIV: HCQ: 1 and placebo: 0; 5. chronic airways disease (asthma, COPD): HCQ: 30 (12.3%) and placebo: 21 (8.5%); 6. chronic liver disease: HCQ: 1 and placebo: 1.
Interventions	Intervention: oral dosing of HCQ: 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) once daily for 4 more days (5 days in total). Placebo: folic acid in the USA and lactose in Canada - unlabelled placebo tablets.
Outcomes	Primary outcomes: initial outcome was the ordinal outcome by day 14 of not hospitalized, hospitalized, or intensive care unit stay or death; however, this was amended on 24 April when fewer patients were hospitalized than anticipated. The primary outcome was therefore change in symptom severity over 14 days as longitudinally measured on a 10-point visual analogue scale. Secondary outcomes: incidence of death and hospitalization, incidence of study medicine withdrawal.
Notes	Dates of recruitment: 22 March to 6 May with follow-up for all outcomes until 15 June 2020.

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Sponsors/funders: Steve Kirsch, Jan and David Baszucki, the Minnesota Chinese Chamber of Commerce, the Alliance of Minnesota Chinese Organizations, and the University of Minnesota Foundation. Canadian funding was received from various sources. In Quebec, funds were received from the Clinical Practice Assessment Unit of the McGill University Health Centre and the McGill Interdisciplinary Initiative in Infection and Immunity's Emergency COVID-19 Research Funding. In Manitoba, research support was received from the Manitoba Medical Service Foundation and Research Manitoba. Purolator Canada provided in-kind courier support for the participating Canadian sites. Apotex Canada and Rising Pharmaceuticals in the USA provided a donation of some of the hydroxychloroquine tablets used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The trial statistician generated a permuted block randomization sequence using differently sized blocks in a 1:1 allocation, stratified by country. A separate randomization stratum also existed for persons who were initially asymptomatic at the time of informed consent but became symptomatic before receiving the study medication on day 1." Appropriate method; adequate description.
Allocation concealment (selection bias)	Low risk	"The research pharmacies held this list, and statisticians verified that the randomization sequence was followed." Appropriate; blinding maintained for investigators and participants.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Appropriate method: the tablets were unmarked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were self-assessed by participants. "We assessed the efficacy of study medicine masking on day 14. Of the 194 participants who completed day-14 surveys in the intervention group, 49% (n = 94) correctly identified that they had received hydroxychloroquine, 7% (n = 14) believed that they had received placebo, and 44% (n = 86) were unsure. Of the 182 who completed day-14 surveys in the placebo group, 30% (n = 54) correctly guessed placebo, 25% (n = 46) incorrectly guessed hydroxychloroquine, 42% (n = 76) were unsure of their randomization assignment, and 3% (n = 6) did not respond. Thus, masking was generally effective, with adverse effects markedly differing between groups."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear for all outcomes. The primary outcome was self-reported by participants, therefore it relied on follow-up data responses. There was significant attrition from enrolment to availability of follow-up data (14%), with similar percentages in each group, but unknown reasons for loss to follow-up. Imputation for missing data in participants who were asymptomatic at baseline or who were hospitalized or died could have mitigated the effect of this, but the number for whom this occurred is not reported. Sensitivity analyses only included different denominators (or used a median in place of mean), rather than imputing data for all missing participants, for the primary outcome of change in severity – only for absolute severity: "An additional sensitivity analysis was performed using overall symptom severity scores (rather than change in scores) and which included the 68 participants with no follow-up symptom data. We generated 1000 estimates from

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Skipper 2020 *(Continued)*

		simple random samples of n=400, and derived a mean difference of -0.17 overall symptom severity with a corresponding 95%CI of -0.39 to 0.06." Adverse events were also conducted on the same subset of participants, with no imputation for missing data. For hospitalization and death, attrition was lower (< 10%) in each arm, though no imputation was conducted.
Selective reporting (reporting bias)	High risk	The change in primary outcome was justified due to low recruitment levels and an inability to attain adequate numbers to reach primary outcome. This was approved by the DSMB, and the final primary outcome was clinically relevant, and a modification of initial secondary outcomes. However, selective reporting of outcomes occurred separately from this, and was not explained: the original ordinal primary outcome was not analysed "because of the low event rate". Despite the low event rate, such an analysis should have been reported in the supplementary appendix.
Other bias	High risk	The trial was terminated early, and as the primary outcome was a longitudinal time-updating variable, this could have led to misleading results.

Tang 2020

Study characteristics	
Methods	RCT comparing outcomes for participants receiving HCQ ("HCQ arm") vs those not receiving HCQ ("standard care arm"). No blinding or placebo. Follow-up: planned PCR on respiratory tract samples on days 4, 7, 10, 14, 21, and 28 from enrolment. "In addition to SARS-CoV-2 testing, patients were assessed on each scheduled visit for vital signs, C reactive protein, erythrocyte sedimentation rate, tumour necrosis factor α, interleukin 6, complete blood cell count with differential, blood chemistry, coagulation panel, pulse oximetry, and respiratory symptoms. Records of administration of hydroxychloroquine and adverse events were reviewed daily to ensure fidelity to the protocol and, more importantly, patient safety. Computed tomography of the chest was assessed on screening and at the last visit of the treatment period (day 14 for patients with mild to moderate disease and day 21 for severe disease)."
Participants	Setting: "16 government designated covid-19 treatment centres in three provinces in China (Hubei, Henan, and Anhui)", China. Number of participants: 150 total: 75 HCQ arm; 75 standard care arm. Inclusion criteria: "age 18 years or older, ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens with RT-PCR, willingness to participate, and consent not to be enrolled in other clinical trials during the study period" Exclusion criteria: "age below 18 years; severe conditions including malignancies, heart, liver, or kidney disease or poorly controlled metabolic diseases; unsuitability for oral administration; pregnancy or lactation; allergy to hydroxychloroquine; inability to cooperate with investigators due to cognitive impairments or poor mental status; severe hepatic impairment (for example, Child-Pugh grade C, ALT more than fivefold the upper limit); and severe renal impairment (eGFR ≤30 mL/min/1.73 m2) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis." Initially excluded patients with severe disease; on 17 February this decision was overturned due to probable anti-inflammatory effects of HCQ being seen as desirable for these patients. Age: HCQ arm: mean 48.0 years (SD 14.1); standard care arm: mean 44.1 years (SD 15.0). Sex: HCQ arm female:male 33:42; standard care arm female:male 35:40.

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	Method of diagnosis: positive RT-PCR for SARS-CoV-2 on upper or lower respiratory tract sample. Clinical presentation: HCQ arm: 15/75 upper respiratory tract illness; 60/75 lower respiratory tract illness. Standard care arm: 7/75 upper respiratory tract illness; 68/75 lower respiratory tract illness. COVID-19 disease severity at presentation: HCQ arm: 15/75 mild; 59/75 moderate; 1/75 severe. Standard care arm: 7/75 mild; 67/75 moderate; 1/75 severe. Time from symptom onset to enrolment: HCQ arm: mean 16.0 days (SD 9.9; 73 participants); standard care arm: mean 17.1 days (SD 11.1; 74 participants). Comorbidities: 6/75 in the HCQ arm and 3/75 in the standard care arm had hypertension; 12/75 in the HCQ arm and 9/75 in the standard care arm had diabetes mellitus. Place of care: all inpatients in hospital.
Interventions	HCQ arm: HCQ 400 mg orally 3 times a day for 3 days, then twice daily from day 4, for a total of 14 days for those with mild/moderate disease, and 21 days for severe disease. 37/75 had umifenovir (Arbidol); 13/75 ribavirin; 13/75 lopinavir/ritonavir; 8/75 oseltamivir; 1/75 entecavir; 6/75 corticosteroids; 32/75 antibacterials. Standard care arm: 33/75 had umifenovir (Arbidol); 15/75 ribavirin; 12/75 lopinavir/ritonavir; 9/75 oseltamivir; 1/75 entecavir; 2/75 ganciclovir; 4/75 corticosteroids; 27/75 antibacterials.
Outcomes	Primary: “negative conversion of SARS-CoV-2 by 28 days and whether patients with severe COVID-19 had clinical improvement by 28 days” (Negative conversion: “two consecutive reports of a negative result for SARS-CoV-2 at least 24 hours apart without a subsequent report of a positive result by the end of the study. We considered the date of the first negative report as the date of negative conversion.”) Changed primary outcome on 17 February (6 days into trial) from “Negative conversion rate by Day 10”. Secondary outcomes: “Probability of negative conversion at day 4, 7, 10, 14, or 21”; adverse events; alleviation of clinical symptoms within 28 days: “resolving from fever to an axillary temperature of 36.6°C or below, normalization of SpO2 (>94% on room air), and disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production, and shortness of breath.” Also planned, but not reported: “probabilities of alleviation of clinical symptoms; improvement of C reactive protein, erythrocyte sedimentation rate, tumour necrosis factor α, interleukin 6, and absolute blood lymphocyte count; improvement of lung lesions on chest radiology; all cause death; and disease progression in patients with mild to moderate disease. The time frame for these secondary outcomes was from randomisation to 28 days.”
Notes	Dates of recruitment: 11 February to 29 February 2020. Sponsors/funders: “Emergent Projects of National Science and Technology (2020YFC0844500), National Natural Science Foundation of China (81970020, 81770025), National Key Research and Development Program of China (2016YFC0901104), Shanghai Municipal Key Clinical Specialty (shslczdzk02202, shslczdzk01103), National Innovative Research Team of High-level Local Universities in Shanghai, Shanghai Key Discipline for Respiratory Diseases (2017ZZ02014), National Major Scientific and Technological Special Project for Significant New Drugs Development (2017ZX09304007), Key Projects in the National Science and Technology Pillar Program during the Thirteenth Five-year Plan Period (2018ZX09206005-004, 2017ZX10202202-005-004, 2017ZX10203201-008)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence. Stratified by disease severity (mild/moderate vs severe) with 1:1 randomization within strata.

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Allocation concealment (selection bias)	Low risk	Cards kept in envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding, but performance bias unlikely.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding, but unlikely to have affected outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition appeared to be low, but is difficult to quantify, with varying denominators, and follow-up beyond 21 days appears low.
Selective reporting (reporting bias)	Unclear risk	The primary outcome was changed during the trial, but a reasonable justification was provided. However, only the primary outcome and adverse events were reported in the final report.
Other bias	High risk	The trial was stopped early, and follow-up was incomplete. This may lead to changes in survival analysis, which is what was employed for the primary outcome of time to negative PCR for SARS-CoV-2.

ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
AZ - Azithromycin
CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration
COPD - Chronic obstructive pulmonary disease
CQ - Chloroquine
CT - Computerized tomography
ECMO - Extracorporeal membrane oxygenation
eGFR - Estimated glomerular filtration rate
FiO2 - Fraction of inspired oxygen
HCQ - Hydroxychloroquine
HIV - Human Immunodeficiency Virus
IgG - Immunoglobulin G
IgM - Immunoglobulin M
ITT - Intention to treat
IQR - Interquartile range
L/min - Litres per minute
LPV/r - Lopinavir/ritonavir
MDRD - Modification of Diet in Renal Disease Study equation
msec - Milliseconds
PaO2 - Partial pressure of oxygen in arterial blood
PCR - Polymerase chain reaction
QTc - Corrected QT interval
QTcF - Corrected QT interval, calculated according to Fridericia's formula
RCT - Randomized controlled trial
RNA - Ribonucleic acid
RT-PCR - Reverse transcription polymerase chain reaction
SaO2 - Saturation of oxygen, ascertained by direct measurement of oxygen bound to haem protein of haemoglobin in the blood
SD - Standard deviation
SOC - Standard of care
SpO2 - Saturation of oxygen, ascertained by indirect measurement of oxygen bound to haem protein of haemoglobin in the blood using pulse oximetry
WHO - World Health Organization

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agrawal 2020	Not an RCT
Alia 2020	Not an RCT
Brown 2020	Not an RCT
ChiCTR2000029542	Not an RCT
ChiCTR2000029609	Not an RCT
ChiCTR2000029898	No control group without CQ/HCQ
ChiCTR2000029899	No control group without CQ/HCQ
Colson 2020a	Not an RCT
Colson 2020b	Not an RCT
EUCTR2020-000890-25-FR	Not an RCT
EUCTR2020-001421-31-ES	No control group without CQ/HCQ
Ferner 2020	Not an RCT
Gao 2020	Not an RCT
Gendrot 2020	Not an RCT
Heldwein 2020	Not an RCT
Lee 2020	Not an RCT
Lofgren 2020	Not an RCT
Nau 2020	Not an RCT
NCT04304053	Duplicate
NCT04321278	No control group without CQ/HCQ
NCT04321993	Not an RCT
NCT04323527	No control group without CQ/HCQ
NCT04326725	Not an RCT
NCT04329572	Not an RCT
NCT04329611	Duplicate
NCT04332094	No control group without CQ/HCQ

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Study	Reason for exclusion
NCT04333225	Not an RCT
NCT04334512	Not an RCT
NCT04335084	Not an RCT
NCT04341493	No control group without CQ/HCQ
NCT04341727	No control group without CQ/HCQ
NCT04343092	No control group without CQ/HCQ
NCT04343677	Trial removed from trial registry.
NCT04344457	Not an RCT
NCT04345419	No control group without CQ/HCQ
NCT04345653	Not an RCT
NCT04346147	No control group without CQ/HCQ
NCT04347798	Not an RCT
NCT04348474	Not an RCT
NCT04350281	No control group without CQ/HCQ
NCT04350450	Not an RCT
NCT04351620	Not an RCT
NCT04351919	Not an RCT
NCT04354870	Not an RCT
NCT04361461	No control group without CQ/HCQ
NCT04362189	No CQ/HCQ
NCT04370262	CQ was part of standard care at the start of the trial, but then abandoned.
NCT04395768	No control group without CQ/HCQ
Pagliano 2020	Not an RCT
Patri 2020	Not an RCT
Principi 2020	Not an RCT
Rathi 2020	Not an RCT
Sahraei 2020	Not an RCT
Yu 2020	Not an RCT

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CQ, chloroquine; HCQ, hydroxychloroquine; RCT, randomized controlled trial

DATA AND ANALYSES

Comparison 1. HCQ versus standard care without HCQ, or placebo, for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death due to any cause	9	8208	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.99, 1.19]
1.2 Death due to any cause (sensitivity analysis)	9	8043	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.99, 1.19]
1.3 Negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment	3	213	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.10]
1.4 Negative PCR for SARS-CoV-2 on respiratory samples at day 7 from enrolment	2	180	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.68, 1.09]
1.5 Proportion admitted to hospital (if receiving ambulatory treatment)	1	465	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.13, 1.27]
1.6 Progression to mechanical ventilation	3	4521	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.91, 1.37]
1.7 Length of hospital admission (in days)	2	642	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.75, 0.45]
1.8 Time to clinical improvement	1		Hazard Ratio (IV, Random, 95% CI)	1.01 [0.59, 1.74]
1.9 Time to negative PCR for SARS-CoV-2 on respiratory samples	1		Hazard Ratio (IV, Random, 95% CI)	0.85 [0.58, 1.23]
1.10 Participants with any adverse events	6	1394	Risk Ratio (M-H, Random, 95% CI)	2.90 [1.49, 5.64]
1.11 Participants with serious adverse events	6	1004	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.37, 1.79]
1.12 Participants with prolongation of QT-interval on electrocardiogram	1	147	Risk Ratio (M-H, Random, 95% CI)	8.47 [1.14, 63.03]

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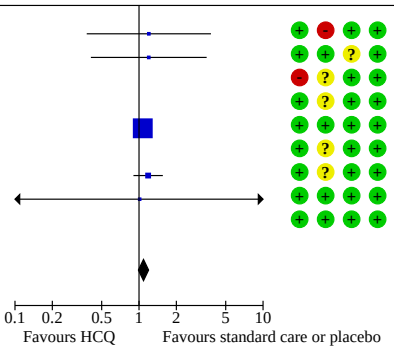
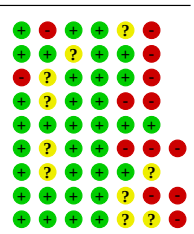
Analysis 1.1. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 1: Death due to any cause

Study or Subgroup	HCQ Events	HCQ Total	Standard care or placebo Events	Standard care or placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Abd-Elsalam 2020	6	97	5	97	0.7%	1.20 [0.38 , 3.80]
Cavalcanti 2020	7	221	6	227	0.8%	1.20 [0.41 , 3.51]
Chen 2020a	0	15	0	15		Not estimable
Chen 2020c	0	21	0	12		Not estimable
Horby 2020	418	1561	788	3155	86.4%	1.07 [0.97 , 1.19]
Mitjà 2020a	0	136	0	157		Not estimable
Pan 2020	104	947	84	906	12.1%	1.18 [0.90 , 1.56]
Skipper 2020	1	244	1	247	0.1%	1.01 [0.06 , 16.09]
Tang 2020	0	75	0	75		Not estimable
Total (95% CI)		**3317**		**4891**	**100.0%**	**1.09 [0.99 , 1.19]**
Total events:	536		884			

Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)
Test for subgroup differences: Not applicable



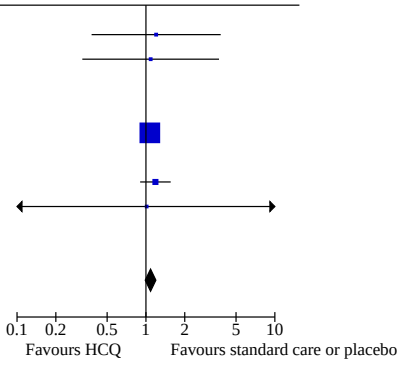


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 2: Death due to any cause (sensitivity analysis)

Study or Subgroup	HCQ Events	HCQ Total	Standard care or placebo Events	Standard care or placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Abd-Elsalam 2020	6	97	5	97	0.7%	1.20 [0.38 , 3.80]
Cavalcanti 2020	5	159	5	173	0.6%	1.09 [0.32 , 3.69]
Chen 2020a	0	15	0	15		Not estimable
Chen 2020c	0	21	0	12		Not estimable
Horby 2020	418	1561	788	3155	86.5%	1.07 [0.97 , 1.19]
Mitjà 2020a	0	122	0	148		Not estimable
Pan 2020	104	947	84	906	12.1%	1.18 [0.90 , 1.56]
Skipper 2020	1	231	1	234	0.1%	1.01 [0.06 , 16.10]
Tang 2020	0	75	0	75		Not estimable
Total (95% CI)		**3228**		**4815**	**100.0%**	**1.09 [0.99 , 1.19]**
Total events:	534		883			

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable



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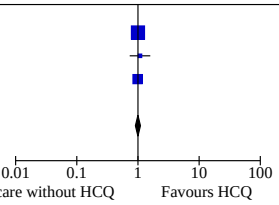
Analysis 1.3. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 3: Negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment

Study or Subgroup	HCQ Events	HCQ Total	Standard care without HCQ Events	Standard care without HCQ Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2020a	15	15	15	15	57.7%	1.00 [0.88 , 1.13]
Chen 2020c	17	21	9	12	6.0%	1.08 [0.73 , 1.59]
Tang 2020	60	75	61	75	36.4%	0.98 [0.84 , 1.15]
Total (95% CI)		**111**		**102**	**100.0%**	**1.00 [0.91 , 1.10]**
Total events:	92		85			

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable

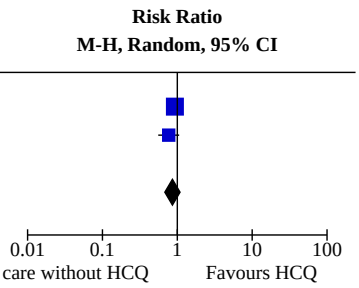


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 4: Negative PCR for SARS-CoV-2 on respiratory samples at day 7 from enrolment

Study or Subgroup	Received HCQ Events	Received HCQ Total	Did not receive HCQ Events	Did not receive HCQ Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2020a	13	15	14	15	60.1%	0.93 [0.73 , 1.18]
Tang 2020	33	75	43	75	39.9%	0.77 [0.56 , 1.06]
Total (95% CI)		**90**		**90**	**100.0%**	**0.86 [0.68 , 1.09]**
Total events:	46		57			

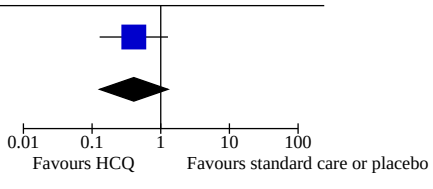
Heterogeneity: Tau² = 0.01; Chi² = 1.40, df = 1 (P = 0.24); I² = 29%
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 5: Proportion admitted to hospital (if receiving ambulatory treatment)

Study or Subgroup	HCQ Events	HCQ Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
Skipper 2020	4	231	10	234	100.0%	0.41 [0.13 , 1.27]
Total (95% CI)		**231**		**234**	**100.0%**	**0.41 [0.13 , 1.27]**
Total events:	4		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



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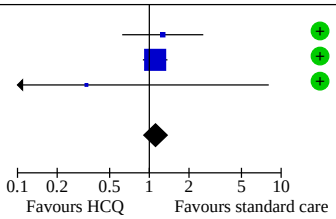
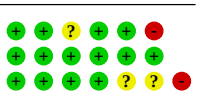
Analysis 1.6. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 6: Progression to mechanical ventilation

Study or Subgroup	HCQ Events	HCQ Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020	16	221	13	227	8.4%	1.26 [0.62 , 2.57]
Horby 2020	118	1300	215	2623	91.2%	1.11 [0.89 , 1.37]
Tang 2020	0	75	1	75	0.4%	0.33 [0.01 , 8.05]
Total (95% CI)		**1596**		**2925**	**100.0%**	**1.11 [0.91 , 1.37]**
Total events:	134		229			

Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



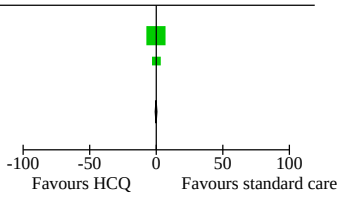


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 7: Length of hospital admission (in days)

Study or Subgroup	HCQ Mean	HCQ SD	HCQ Total	Standard care Mean	Standard care SD	Standard care Total	Weight	Mean Difference IV, Random, 95% CI
Abd-Elsalam 2020	11.04	2.71	97	11.27	2.19	97	75.7%	-0.23 [-0.92 , 0.46]
Cavalcanti 2020	8.9	6.2	221	8.8	7	227	24.3%	0.10 [-1.12 , 1.32]
Total (95% CI)			**318**			**324**	**100.0%**	**-0.15 [-0.75 , 0.45]**

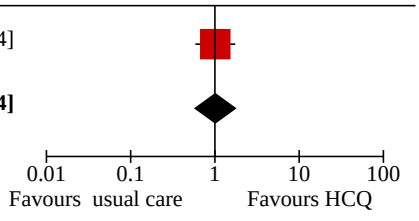
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 8: Time to clinical improvement

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Tang 2020	0.00995	0.278	100.0%	1.01 [0.59 , 1.74]
Total (95% CI)			**100.0%**	**1.01 [0.59 , 1.74]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



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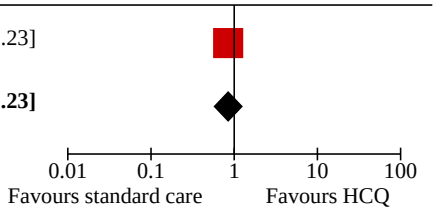
Analysis 1.9. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 9: Time to negative PCR for SARS-CoV-2 on respiratory samples

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Tang 2020	-0.167236	0.191774	100.0%	0.85 [0.58 , 1.23]
Total (95% CI)			**100.0%**	**0.85 [0.58 , 1.23]**

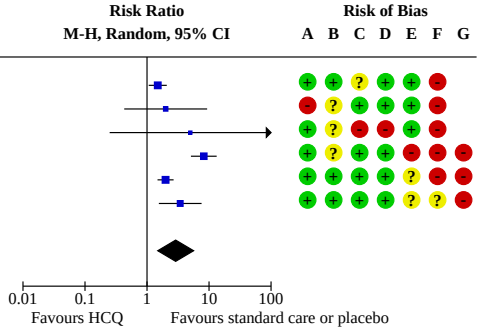
Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 10: Participants with any adverse events

Study or Subgroup	HCQ Events	HCQ Total	Standard care or placebo Events	Standard care or placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020 (1)	67	199	40	177	22.8%	1.49 [1.07 , 2.08]
Chen 2020a (2)	4	15	2	15	10.5%	2.00 [0.43 , 9.32]
Chen 2020b	2	31	0	31	4.1%	5.00 [0.25 , 100.08]
Mitjà 2020a (3)	121	169	16	184	21.5%	8.23 [5.11 , 13.28]
Skipper 2020 (4)	92	212	46	211	23.1%	1.99 [1.48 , 2.68]
Tang 2020 (5)	21	70	7	80	18.0%	3.43 [1.55 , 7.58]
Total (95% CI)		**696**		**698**	**100.0%**	**2.90 [1.49 , 5.64]**
Total events:	307		111			

Heterogeneity: Tau² = 0.48; Chi² = 38.18, df = 5 (P < 0.00001); I² = 87%
Test for overall effect: Z = 3.13 (P = 0.002)
Test for subgroup differences: Not applicable



Footnotes

(1) Cavalcanti 2020 - safety population included participants who received at least one dose of HCQ, and participants who received neither HCQ nor azithromycin.
(2) Chen 2020a and Chen 2020b - safety population assumed to be the same as ITT population. All participants assumed to have received treatment according to group they were randomised to
(3) Mitjà 2020 - safety population was based on participants randomised to each group, rather than participants who received the study drug.
(4) Skipper 2020 - Safety population excludes participants with no follow up data, and those with only vital status data, including deaths.
(5) Tang 2020 - Safety population based on all those who received at least one dose of HCQ versus all those who received no HCQ.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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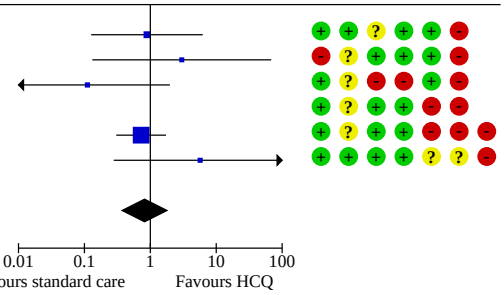
Analysis 1.11. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 11: Participants with serious adverse events

Study or Subgroup	HCQ Events	HCQ Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020 (1)	2	199	2	177	15.4%	0.89 [0.13 , 6.25]
Chen 2020a (2)	1	15	0	15	6.2%	3.00 [0.13 , 68.26]
Chen 2020b	0	31	4	31	7.2%	0.11 [0.01 , 1.98]
Chen 2020c	0	21	0	12		Not estimable
Mitjà 2020a	8	169	12	184	64.6%	0.73 [0.30 , 1.73]
Tang 2020 (3)	2	70	0	80	6.6%	5.70 [0.28 , 116.84]
Total (95% CI)		**505**		**499**	**100.0%**	**0.82 [0.37 , 1.79]**
Total events:	13		18			

Heterogeneity: Tau² = 0.05; Chi² = 4.18, df = 4 (P = 0.38); I² = 4%
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable



Footnotes

(1) Cavalcanti 2020 - safety population included participants who received at least one dose of HCQ, and participants who received neither HCQ nor azithromycin.
(2) Chen 2020a and Chen 2020b - safety population assumed to be the same as ITT population. All participants assumed to have received treatment according to group they were ra
(3) Tang 2020 - Safety population based on all those who received at least one dose of HCQ versus all those who received no HCQ.

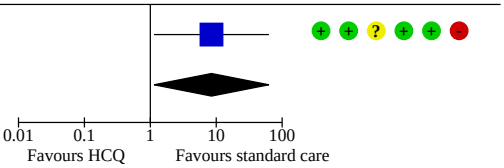
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.12. Comparison 1: HCQ versus standard care without HCQ, or placebo, for treatment, Outcome 12: Participants with prolongation of QT-interval on electrocardiogram

Study or Subgroup	HCQ Events	HCQ Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020	13	89	1	58	100.0%	8.47 [1.14 , 63.03]
Total (95% CI)		**89**		**58**	**100.0%**	**8.47 [1.14 , 63.03]**
Total events:	13		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.09 (P = 0.04)
Test for subgroup differences: Not applicable



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. CQ versus lopinavir/ritonavir for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Negative PCR for SARS-CoV-2 on respiratory samples at day 7 from enrolment	1	22	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.64, 2.25]

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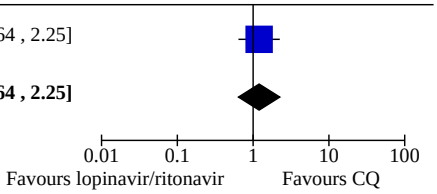
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment	1	22	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.85, 1.36]
2.3 Discharge from hospital at day 14 from enrolment	1	22	Risk Ratio (M-H, Random, 95% CI)	1.91 [1.09, 3.34]
2.4 Clinical improvement at day 10 from enrolment	1	22	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.78, 2.42]
2.5 Total adverse events	1	22	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.78, 1.50]
2.6 Serious adverse events	1	22	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Analysis 2.1. Comparison 2: CQ versus lopinavir/ritonavir for treatment, Outcome 1: Negative PCR for SARS-CoV-2 on respiratory samples at day 7 from enrolment

Study or Subgroup	CQ Events	CQ Total	Lopinavir/ritonavir Events	Lopinavir/ritonavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Huang 2020	7	10	7	12	100.0%	1.20 [0.64 , 2.25]
Total (95% CI)		**10**		**12**	**100.0%**	**1.20 [0.64 , 2.25]**
Total events:	7		7			

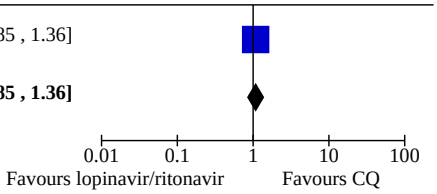
Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: CQ versus lopinavir/ritonavir for treatment, Outcome 2: Negative PCR for SARS-CoV-2 on respiratory samples at day 14 from enrolment

Study or Subgroup	CQ Events	CQ Total	Lopinavir/ritonavir Events	Lopinavir/ritonavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Huang 2020	10	10	11	12	100.0%	1.08 [0.85 , 1.36]
Total (95% CI)		**10**		**12**	**100.0%**	**1.08 [0.85 , 1.36]**
Total events:	10		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



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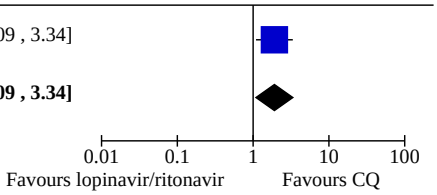
Analysis 2.3. Comparison 2: CQ versus lopinavir/ritonavir for treatment, Outcome 3: Discharge from hospital at day 14 from enrolment

Study or Subgroup	CQ Events	CQ Total	Lopinavir/ritonavir Events	Lopinavir/ritonavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Huang 2020	10	10	6	12	100.0%	1.91 [1.09 , 3.34]
Total (95% CI)		**10**		**12**	**100.0%**	**1.91 [1.09 , 3.34]**
Total events:	10		6			

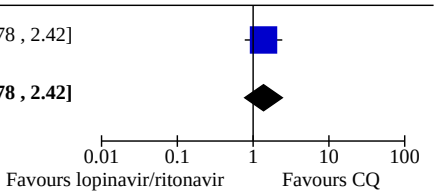
Heterogeneity: Not applicable
Test for overall effect: Z = 2.27 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: CQ versus lopinavir/ritonavir for treatment, Outcome 4: Clinical improvement at day 10 from enrolment

Study or Subgroup	CQ Events	CQ Total	Lopinavir/ritonavir Events	Lopinavir/ritonavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Huang 2020	8	10	7	12	100.0%	1.37 [0.78 , 2.42]
Total (95% CI)		**10**		**12**	**100.0%**	**1.37 [0.78 , 2.42]**
Total events:	8		7			

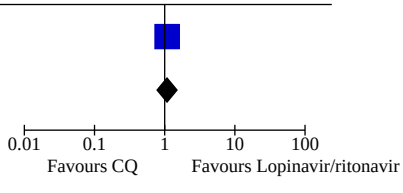
Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: CQ versus lopinavir/ritonavir for treatment, Outcome 5: Total adverse events

Study or Subgroup	CQ Events	CQ Total	Lopinavir/ritonavir Events	Lopinavir/ritonavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Huang 2020	9	10	10	12	100.0%	1.08 [0.78 , 1.50]
Total (95% CI)		**10**		**12**	**100.0%**	**1.08 [0.78 , 1.50]**
Total events:	9		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable



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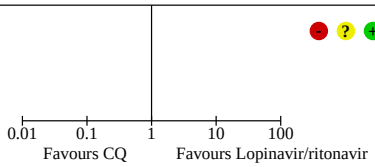
Analysis 2.6. Comparison 2: CQ versus lopinavir/ritonavir for treatment, Outcome 6: Serious adverse events

Study or Subgroup	CQ Events	CQ Total	Lopinavir/ritonavir Events	Lopinavir/ritonavir Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Huang 2020	0	10	0	12		Not estimable		- ? + + + -
Total (95% CI)		**10**		**12**		**Not estimable**		
Total events:	0		0					

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

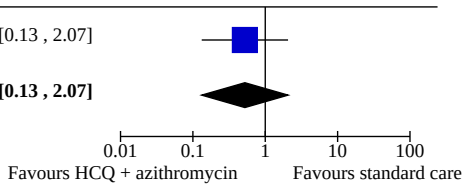
Comparison 3. HCQ + azithromycin versus standard care for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Death due to any cause	1	444	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.13, 2.07]
3.2 Progression to mechanical ventilation	1	444	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.82, 3.15]
3.3 Length of hospital stay in days	1	444	Mean Difference (IV, Random, 95% CI)	0.50 [-0.81, 1.81]
3.4 Participants with any adverse events	1	416	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.27, 2.38]
3.5 Participants with serious adverse events	1	416	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.36, 9.43]
3.6 Participants with prolongation of QT-interval on electrocardiogram	1	174	Risk Ratio (M-H, Random, 95% CI)	8.50 [1.16, 62.31]

Analysis 3.1. Comparison 3: HCQ + azithromycin versus standard care for treatment, Outcome 1: Death due to any cause

Study or Subgroup	HCQ+azithromycin Events	HCQ+azithromycin Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020	3	217	6	227	100.0%	0.52 [0.13 , 2.07]	
Total (95% CI)		**217**		**227**	**100.0%**	**0.52 [0.13 , 2.07]**	
Total events:	3		6				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



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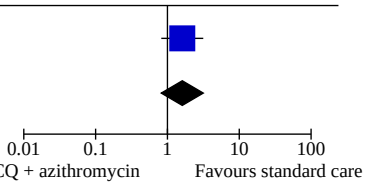
Analysis 3.2. Comparison 3: HCQ + azithromycin versus standard care for treatment, Outcome 2: Progression to mechanical ventilation

Study or Subgroup	HCQ + azithromycin Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020	20	217	13	227	100.0%	1.61 [0.82 , 3.15]
Total (95% CI)		**217**		**227**	**100.0%**	**1.61 [0.82 , 3.15]**
Total events:	20		13			

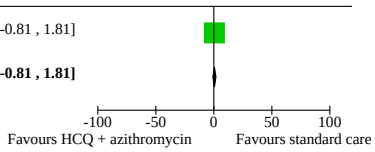
Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.17)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: HCQ + azithromycin versus standard care for treatment, Outcome 3: Length of hospital stay in days

Study or Subgroup	HCQ + azithromycin Mean [Days]	SD [Days]	Total	Standard Care Mean [Days]	SD [Days]	Total	Weight	Mean Difference IV, Random, 95% CI [Days]
Cavalcanti 2020	9.4	7.8	217	8.9	6.2	227	100.0%	0.50 [-0.81 , 1.81]
Total (95% CI)			**217**			**227**	**100.0%**	**0.50 [-0.81 , 1.81]**

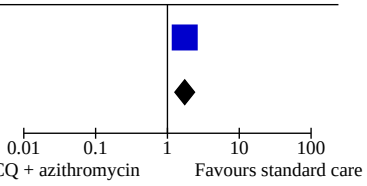
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: HCQ + azithromycin versus standard care for treatment, Outcome 4: Participants with any adverse events

Study or Subgroup	HCQ + azithromycin Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020 (1)	94	239	40	177	100.0%	1.74 [1.27 , 2.38]
Total (95% CI)		**239**		**177**	**100.0%**	**1.74 [1.27 , 2.38]**
Total events:	94		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.45 (P = 0.0006)
Test for subgroup differences: Not applicable



Footnotes

(1) The safety population in this trial included participants who received at least one dose of HCQ and azithromycin, versus participants who received neither HCQ n

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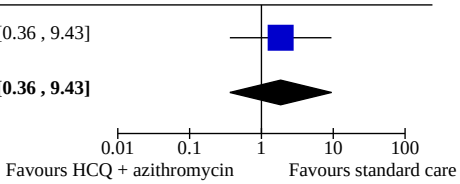
Analysis 3.5. Comparison 3: HCQ + azithromycin versus standard care for treatment, Outcome 5: Participants with serious adverse events

Study or Subgroup	HCQ + azithromycin Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020 (1)	5	239	2	177	100.0%	1.85 [0.36 , 9.43]
Total (95% CI)		**239**		**177**	**100.0%**	**1.85 [0.36 , 9.43]**
Total events:	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable

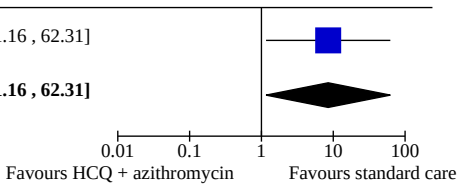


Footnotes
(1) The safety population in this trial included participants who received at least one dose of HCQ and azithromycin, versus participants who received neither HCQ n

Analysis 3.6. Comparison 3: HCQ + azithromycin versus standard care for treatment, Outcome 6: Participants with prolongation of QT-interval on electrocardiogram

Study or Subgroup	HCQ + azithromycin Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cavalcanti 2020 (1)	17	116	1	58	100.0%	8.50 [1.16 , 62.31]
Total (95% CI)		**116**		**58**	**100.0%**	**8.50 [1.16 , 62.31]**
Total events:	17		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.04)
Test for subgroup differences: Not applicable



Footnotes
(1) The safety population in this trial included participants who received at least one dose of HCQ and azithromycin, versus participants who received neither HCQ n

Comparison 4. HCQ versus febuxostat for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Death due to any cause	1	54	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.2 Admission to hospital	1	54	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.26, 5.24]

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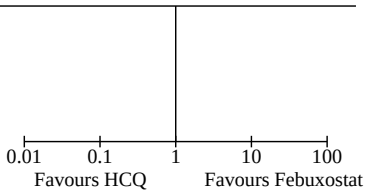
Analysis 4.1. Comparison 4: HCQ versus febuxostat for treatment, Outcome 1: Death due to any cause

Study or Subgroup	HCQ Events	HCQ Total	Febuxostat Events	Febuxostat Total	Weight	Risk Ratio M-H, Random, 95% CI
Davoodi 2020	0	25	0	29		Not estimable
Total (95% CI)		**25**		**29**		**Not estimable**
Total events:	0		0			

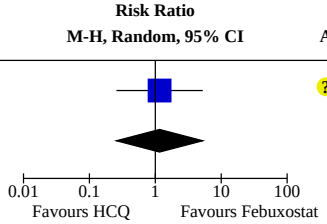
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

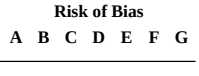


Analysis 4.2. Comparison 4: HCQ versus febuxostat for treatment, Outcome 2: Admission to hospital

Study or Subgroup	HCQ Events	HCQ Total	Febuxostat Events	Febuxostat Total	Weight	Risk Ratio M-H, Random, 95% CI
Davoodi 2020	3	25	3	29	100.0%	1.16 [0.26 , 5.24]
Total (95% CI)		**25**		**29**	**100.0%**	**1.16 [0.26 , 5.24]**
Total events:	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 5. HCQ versus placebo for postexposure prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Development of confirmed COVID-19 at 14 days from enrolment	1	821	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.50, 2.87]
5.2 Patients hospitalized due to COVID-19	1	821	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.66]
5.3 Participants with any adverse events	1	700	Risk Ratio (M-H, Random, 95% CI)	2.39 [1.83, 3.11]
5.4 Participants with serious adverse events	1	700	Risk Ratio (M-H, Random, 95% CI)	Not estimable

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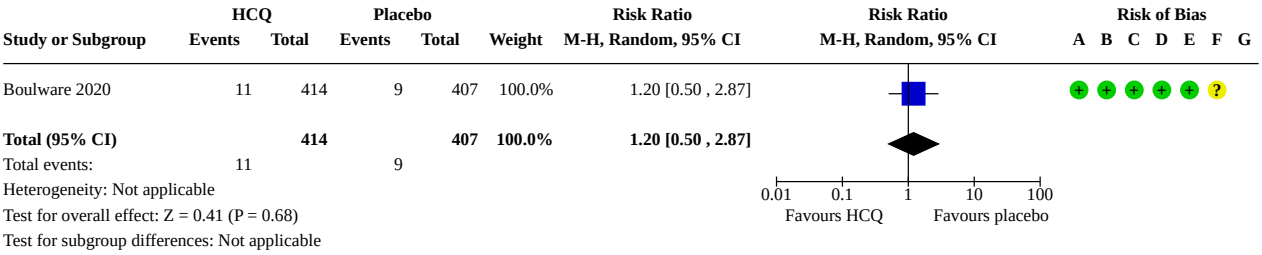
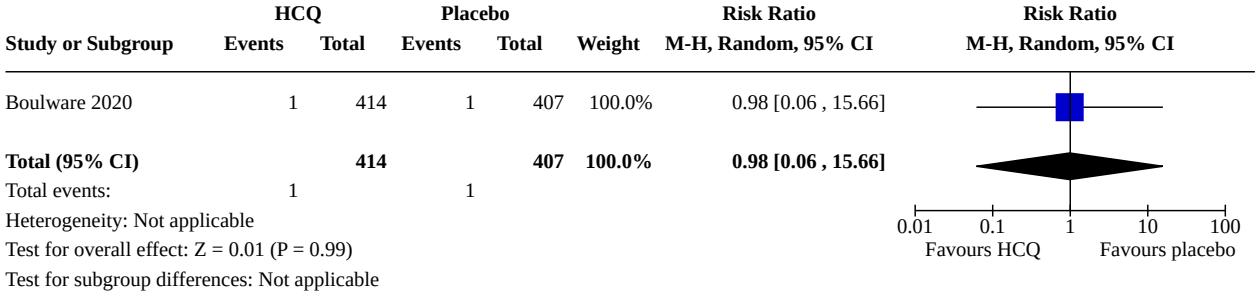
Analysis 5.1. Comparison 5: HCQ versus placebo for postexposure prophylaxis, Outcome 1: Development of confirmed COVID-19 at 14 days from enrolment

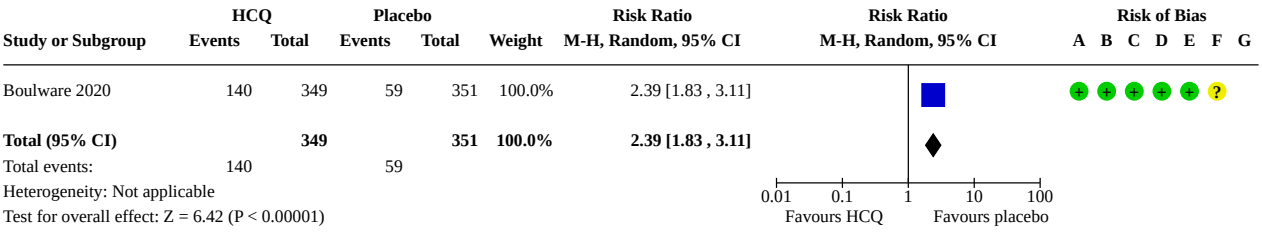


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.2. Comparison 5: HCQ versus placebo for postexposure prophylaxis, Outcome 2: Patients hospitalized due to COVID-19



Analysis 5.3. Comparison 5: HCQ versus placebo for postexposure prophylaxis, Outcome 3: Participants with any adverse events



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

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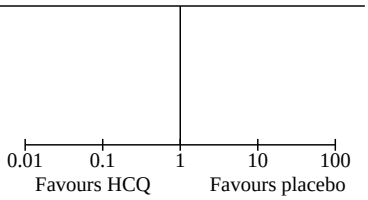
Analysis 5.4. Comparison 5: HCQ versus placebo for postexposure prophylaxis, Outcome 4: Participants with serious adverse events

Study or Subgroup	HCQ Events	HCQ Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Boulware 2020	0	349	0	351		Not estimable
Total (95% CI)		**349**		**351**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Ongoing trials for treatment: actively recruiting or completed; not yet published

Trial registration number; trial registry	Location(s)	Interventions; abbreviated name	Recruitment status	Estimated completion	Target enrolment
NCT02735707 ClinicalTrials.gov	13 countries; registered in the Netherlands	Adaptive platform trial including HCQ, or HCQ + lopinavir/ritonavir, vs no HCQ REMAP-CAP	Recruiting	December 2021	7100
NCT04351724 ClinicalTrials.gov	Austria	Platform trial including CQ/HCQ vs placebo ACOVACT	Recruiting	December 2020	500
NCT04328012 ClinicalTrials.gov	USA	Pragmatic adaptive HCQ vs lopinavir/ritonavir vs losartan vs placebo COVID MED	Recruiting	January 2021	4000
NCT04334382 ClinicalTrials.gov	USA	HCQ vs azithromycin HyAzOUT	Recruiting	December 2020	1550
NCT04332991 ClinicalTrials.gov	USA	HCQ vs placebo for hospitalized patients with COVID-19 ORCHID	Completed	April 2021	510
NCT04363827 ClinicalTrials.gov	Italy	HCQ vs observation PROTECT	Recruiting	September 2020	2300
NCT04359953 ClinicalTrials.gov	France	HCQ vs telmisartan vs azithromycin	Recruiting	June 2021	1600
NCT04356495 ClinicalTrials.gov	France	HCQ vs favipiravir vs imatinib vs telmisartan vs placebo COVERAGE	Recruiting	July 2020	1057

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Table 1. Ongoing trials for treatment: actively recruiting or completed; not yet published *(Continued)*

PACTR202004801273802 Pan African Clinical Trials Registry	Nigeria	CQ vs HCQ vs placebo	Recruiting	October 2020	600
ISRCTN86534580 ISRCTN registry	UK	HCQ vs standard care for treatment	Recruiting	March 2021	3000
NCT04324463 ClinicalTrials.gov	Canada	Azithromycin plus hydroxychloroquine or chloroquine (AZCT) vs AZCT plus interferon beta vs interferon beta vs usual care	Recruiting	September 2020	1500
NCT04345289 ClinicalTrials.gov	Denmark	Convalescent plasma vs sarilumab vs HCQ vs baricitinib vs intravenous and subcutaneous placebo vs oral placebo	Recruiting	June 2021	1500
NCT04358068 ClinicalTrials.gov	USA and Puerto Rico	HCQ vs azithromycin	Completed	October 2020	2000
NCT04340544 ClinicalTrials.gov	Germany	HCQ vs placebo	Recruiting	November 2021	2700
NCT04338698 ClinicalTrials.gov	Pakistan	HCQ vs oseltamivir vs azithromycin	Recruiting	September 2020	500
NCT04353037 ClinicalTrials.gov	USA	HCQ vs placebo	Recruiting	April 2021	850
NCT04321616 ClinicalTrials.gov	Norway	HCQ vs remdesivir vs standard care	Recruiting	August 2020	700
ACTRN12620000445976 ANZCTR	Australia and New Zealand	HCQ vs lopinavir/ritonavir vs HCQ plus lopinavir/ritonavir vs standard care	Recruiting	Not reported	2500
NCT04315948 ClinicalTrials.gov	France and Luxembourg	HCQ vs remdesivir vs lopinavir/ritonavir vs interferon beta-1A vs standard care	Recruiting	March 2023	3100
UTN-A27736297878 Ensaiosclinicos.gov.br	Brazil	HCQ vs placebo	Recruiting	July 2020	1300
NCT04410562 ClinicalTrials.gov	Spain	HCQ vs placebo (pregnant women)	Recruiting	May 2021	714
NCT04392973 ClinicalTrials.gov	Saudi Arabia	HCQ with favipiravir vs standard care	Recruiting	November 2021	520

CQ, chloroquine; HCQ, hydroxychloroquine

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Table 2. Ongoing trials for prevention: actively recruiting or completed; not yet published

Trial registration number; trial registry	Location(s)	Interventions; population; abbreviated name	Recruitment status	Estimated completion	Target enrolment
NCT04333732 ClinicalTrials.gov	USA	Low-/medium-/high-dose chloroquine vs placebo Healthcare workers	Recruiting	February 2021	55,000
NCT04303507 ClinicalTrials.gov	Europe, Asia, Africa	HQC vs CQ vs placebo Healthcare workers COPCOV	Recruiting	April 2021	40,000
NCT04334928 ClinicalTrials.gov	Spain	Emtricitabine/tenofovir (Truvada) vs HCQ vs Truvada + HCQ vs placebo Healthcare workers EPICOS	Recruiting	June 2020	4000
NCT04334148 ClinicalTrials.gov	USA	HCQ vs placebo Healthcare workers	Recruiting	July 2020	15,000
NCT04363450 ClinicalTrials.gov	USA	HCQ vs placebo Healthcare workers (pre-exposure) HCQPreP	Recruiting	July 2020	1700
NCT04318444 ClinicalTrials.gov	USA	HCQ vs placebo Household contacts (postexposure)	Recruiting	March 2021	1600
NCT04341441 ClinicalTrials.gov	USA	Daily HCQ vs weekly HCQ vs placebo Healthcare workers and first responders	Recruiting	June 2020	3000
IRCT20190122042450N4 Iranian Clinical Trials Registry	Iran	HCQ vs no HCQ All contacts (postexposure)	Completed	Not reported	1000
ISRCTN14326006 ISRCTN registry	Canada	HCQ vs placebo Healthcare workers	Recruiting	January 2022	988
NCT04363827 ClinicalTrials.gov	Italy	HCQ vs no HCQ All contacts	Recruiting	September 2020	2300
NCT04352933 ClinicalTrials.gov	UK	HCQ weekly vs HCQ daily vs placebo	Recruiting	October 2020	1000

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Table 2. Ongoing trials for prevention: actively recruiting or completed; not yet published *(Continued)*

		Healthcare workers			
NCT04353037 ClinicalTrials.gov	USA	HCQ vs placebo Healthcare workers	Recruiting	April 2021	850
ACTRN12620000501943 ANZCTR	Australia	HCQ vs placebo Healthcare workers	Recruiting	December 2020	2250
NCT04374942 ClinicalTrials.gov	USA	HCQ vs placebo Healthcare workers	Recruiting	January 2022	988
EudraCT 2020-001987-28 EudraCT	Italy	HCQ vs no HCQ Healthcare workers	Recruiting	Not reported	1000

CQ, chloroquine; HCQ, hydroxychloroquine

Table 3. Summary of characteristics of included studies

Study	Objective; comparisons	Study design	Countries; recruitment dates	Age	Number of participants in primary comparison	Types of participant at enrolment (type of contact; place of care; disease severity)
Abd-El-salam 2020	1: Treatment 1: HCQ vs standard care	RCT, open-label	Egypt March to June 2020	HCQ: mean 40.4 y (SD 18.7 y) Standard care: mean 41.1 y (SD 20.1 y)	194 total: 97 HCQ; 97 standard care	All hospitalized. "The patients were randomized equally between the two groups regarding the disease severity." (Numbers not reported.)
Boulware 2020	3: Postexposure prophylaxis 5: HCQ vs placebo (individually randomized)	RCT, double-blind	USA and Canada 17 March to 6 May 2020	HCQ: median 41 y (IQR 33 to 51) Placebo: median 40 y (IQR 32 to 50)	821 total: 414 HCQ; 407 placebo	HCQ: 275 healthcare contacts; 125 household contacts; 14 NR Placebo: 270 healthcare contacts; 120 household contacts; 17 NR
Cavalcanti 2020	1: Treatment 1: HCQ vs standard care 3: HCQ + azithromycin vs standard care	RCT, open-label	Brazil 29 March to 17 May 2020	HCQ + azithromycin: mean 49.6 y (SD 14.2 y) HCQ: mean 51.3 y (SD 14.5 y) Standard care: mean 49.9 y (SD 15.1 y)	665 total: 217 HCQ + azithromycin; 221 HCQ; 227 standard care	All hospitalized. HCQ + azithromycin: 125/217 mild; 92/217 moderate disease HCQ: 132/221 mild; 89/221 moderate disease Standard care: 130/227 mild; 97/227 moderate disease
Chen 2020a	1: Treatment	RCT, open-label	China	HCQ: mean 50.5 y (SD 3.8 y)	30 total: 15 HCQ; 15	All hospitalized.

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Table 3. Summary of characteristics of included studies *(Continued)*

	1: HCQ vs standard care		6 February to 25 February 2020	Standard care: mean 46.7 y (SD 3.6 y)	standard care	All 30 participants had moderate disease.
Chen 2020b	1: Treatment 1: HCQ vs standard care	RCT, double-blind (no placebo)	China 4 February to 28 February 2020	HCQ: mean 44.1 y (SD 16.1 y) Standard care: mean 45.2 y (SD 14.7 y)	62 total: 31 HCQ; 31 standard care	All hospitalized. All 62 participants had mild disease.
Chen 2020c	1: Treatment 1: HCQ vs standard care	RCT, open-label	Taiwan 1 April to 31 May 2020	HCQ: mean 33 y (SD 12 y) Standard care: mean 32.8 y (SD 8.3 y)	33 total: 21 HCQ; 12 standard care	All hospitalized. HCQ: 19/21 mild; 2/21 moderate Standard care: 10/12 mild; 2/12 moderate
Davoodi 2020	1: Treatment 4: HCQ vs febuxostat	RCT, open-label	Iran 16 March to 10 April 2020	HCQ: mean 57.3 y (standard error 2.2 y) Febuxostat: mean 58 y (standard error 1.47 y)	54 total: 25 HCQ; 29 febuxostat	All ambulatory patients, symptomatic, with abnormalities on CT scan of the chest, but no features of severe acute illness or severe underlying chronic disease.
Horby 2020	1: Treatment 1: HCQ vs standard care	RCT, open-label	UK 25 March to 5 June 2020	HCQ: mean 65.2 y (SD 15.2 y) Standard care: mean 65.4 y (SD 15.4 y)	4716 total: 1561 HCQ; 3155 standard care	All hospitalized. Inferred from level of oxygen/respiratory support need: HCQ: 362/1561 asymptomatic/mild (no oxygen received); 938/1561 moderate/severe (received oxygen); 261/1561 critical disease (invasive ventilation) Standard care: 750/3155 asymptomatic/mild (no oxygen received); 1873/3155 moderate/severe (received oxygen); 532/3155 critical disease (invasive ventilation)
Huang 2020	1: Treatment 2: CQ vs lopinavir/ritonavir (LPV/r)	RCT, open-label	China 27 January to 15 February 2020	CQ: median 41.5 y (IQR 33.8 to 50 y) LPV/r: median 53 y (IQR 41.8 to 63.5 y)	22 total: 10 CQ; 12 LPV/r	All hospitalized. CQ: 7/10 moderate; 3/10 severe disease LPV/r: 7/12 moderate; 5/12 severe disease
Mitjà 2020a	1: Treatment 1: HCQ vs standard care	RCT, open-label	Spain 17 March to 26 May 2020	HCQ: mean 41.6 y (SD 12.4 y) Standard care: mean 41.7 y (SD 12.6 y)	293 total: 136 HCQ; 157 standard care	All ambulatory patients with mild disease, except for 1 patient with severe disease included in the HCQ arm, despite this being an exclusion criterion (included in ITT analysis).
Mitjà 2020b	3: Postexposure prophylaxis	Cluster-RCT, open-label	Spain	HCQ: mean 48.6 y (SD 18.7 y)	2525 total: 1225 HCQ;	HCQ: 131 (12%) healthcare workers; 302 (27%) household contacts; 550

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Table 3. Summary of characteristics of included studies *(Continued)*

	6: HCQ vs standard care (cluster randomized)		17 March to 28 April 2020	Standard care: mean 48.7 y (SD 19.3 y)	1300 standard care	(49%) nursing home workers; 133 (12%) nursing home residents Standard care: 130 (11%) healthcare workers; 338 (28%) household contacts; 584 (49%) nursing home workers; 160 (13%) nursing home residents
Pan 2020	1: Treatment 1: HCQ vs standard care	RCT, open-label	30, across all WHO regions 22 March to 18 June 2020	HCQ: 335 (< 50 years), 410 (50 to 69 years), 202 (≥ 70 years) Standard care: 317 (< 50 years), 396 (50 to 69 years), 193 (≥ 70 years)	1853 total: 947 HCQ; 906 standard care	All hospitalized. HCQ: 862/947 moderate or severe (of whom 517 receiving oxygen), 85 critical Standard care: 824/906 moderate or severe (of whom 483 receiving oxygen), 82 critical
Skipper 2020	1: Treatment 1: HCQ vs placebo	RCT, double-blind	USA and Canada 22 March to 6 May 2020	HCQ: median 41 y (IQR 33 to 49 y) Placebo: median 39 y (IQR 31 to 50 y)	491 total: 244 HCQ; 247 placebo	All ambulatory patients, so presumed to have mild disease if symptomatic. HCQ: 48/244 asymptomatic Placebo: 52/247 asymptomatic
Tang 2020	1: Treatment 1: HCQ vs standard care	RCT, open-label (no placebo)	China 11 February to 29 February 2020	HCQ: mean 48 y (SD 14.1 y) Standard care: mean 44.1 y (SD 15 y)	150 total: 75 HCQ; 75 standard care	All hospitalized. HCQ: 15/75 mild; 59/75 moderate; 1/75 severe disease Standard care: 7/75 mild; 67/75 moderate; 1/75 severe disease

CQ: chloroquine; CT: computed tomography; HCQ: hydroxychloroquine; IQR: interquartile range; ITT: intention-to-treat; NR: not reported; RCT: randomized controlled trial; SD: standard deviation; WHO: World Health Organization; y: years.

Table 4. Dosing regimens in hydroxychloroquine treatment trials[1]

Study	Hydroxychloroquine (HCQ) dose regimen	Control group	Total hydroxychloroquine dose
Abd-Elsalam 2020	800 mg on day 1, followed by 400 mg daily for further 14 days (total duration of treatment 15 days)	Standard care	6400 mg
Cavalcanti 2020 [2]	400 mg orally twice daily for 7 days	Standard care	5600 mg
Chen 2020a [3]	400 mg once daily for 5 days	Standard care	2000 mg
Chen 2020b	200 mg orally twice daily for 5 days	Standard care	2000 mg
Chen 2020c	800 mg on day 1, followed by 400 mg daily for further 6 days (total duration of treatment 7 days)	Standard care	3200 mg
Davoodi 2020	200 mg orally twice daily for 5 days	Standard care	2000 mg

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Table 4. Dosing regimens in hydroxychloroquine treatment trials[1] *(Continued)*

Horby 2020	800 mg at 0 and 6 hours, then 400 mg at 12 hours from first dose and every 12 hourly for 10 days	Standard care	10,000 mg
Mitjà 2020a	800 mg on day 1, followed by 400 mg daily for further 6 days (total duration of treatment 7 days)	Standard care	3200 mg
Pan 2020	2000 mg on day 1, followed by 800 mg daily for further 9 days (total duration of treatment 10 days)	Standard care	9200 mg
Skipper 2020	800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) once daily for 4 more days (5 days in total)	Placebo: folic acid in USA and lactose in Canada	3800 mg
Tang 2020	400 mg orally 3 times a day for 3 days, then twice daily from day 4, for a total of 14 days for those with mild/moderate disease and 21 days for those with severe disease	Standard care	12,400 mg mild/moderate disease; 18,000 mg severe disease

[1]See Table 5 for co-interventions given in each trial.
[2] Cavalcanti 2020 - hydroxychloroquine plus azithromycin group received HCQ 400 mg orally twice daily and azithromycin 500 mg orally once daily for seven days.
[3] Chen 2020a - additionally, all participants in the HCQ arm had nebulized interferon alpha; 12/15 had umifenovir (Arbidol). Standard care arm: no HCQ; all had nebulized interferon alpha; 10/15 had umifenovir (Arbidol).

Table 5. Pharmacological co-interventions given in treatment trials for comparison 1 (HCQ versus standard care or placebo)

Study	Co-interventions in HCQ arm	Co-interventions in comparator arm
Abd-Elsalam 2020	Authors report: "The Egyptian Ministry of Health (MOH) adopted a standard of care treatment protocol for COVID-19 patients. It included paracetamol, oxygen, fluids (according to assessment), empiric antibiotic (cephalosporins), oseltamivir if needed (75 mg/12 hours for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO2 < 60 mmHg, O2 saturation < 90% despite oxygen or noninvasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock".	
Cavalcanti 2020 [1]	Corticosteroids 5/221	Corticosteroids 8/227
	Oseltamivir 38/221	Oseltamivir 51/227
	Aciclovir 1/221	Aciclovir 0/227
	Lopinavir/ritonavir 0/221	Lopinavir/ritonavir 0/227
	Ceftriaxone 86/221	Ceftriaxone 99/227
	Ceftaroline 11/221	Ceftaroline 17/227
	Piperacillin/tazobactam 8/221	Piperacillin/tazobactam 15/227
	Oxacillin 0/221	Oxacillin 1/227
	Vancomycin 1/221	Vancomycin 4/227
	Carbapenem 6/221	Carbapenem 3/227
	Quinolone 22/221	Quinolone 28/227

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Table 5. Pharmacological co-interventions given in treatment trials for comparison 1 (HCQ versus standard care or placebo) *(Continued)*

	No other antiviral, antibiotic, or corticosteroids 21/221	No other antiviral, antibiotic, or corticosteroids 18/227
Chen 2020a [2]	Nebulized interferon alpha 15/15 Umifenovir 12/15	Nebulized interferon alpha 15/15 Umifenovir 10/15
Chen 2020b	Authors report "all received the standard treatment (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids)".	
Chen 2020c [3]	Azithromycin 1/21	Azithromycin 2/12
Horby 2020 [4]	Dexamethasone 8% Azithromycin 17%	Dexamethasone 9% Azithromycin 19%
Mitjà 2020a [5]	Cobicistat-boosted darunavir 49/136	Cobicistat-boosted darunavir 0/157
Pan 2020	The authors report that co-medications will appear in supplementary tables, but these are not provided with the currently available preprint publication.	
Skipper 2020 [6]	Zinc 63/212 Vitamin C 101/212	Zinc 53/211 Vitamin C 101/211
Tang 2020	Umifenovir 37/75 Ribavirin 13/75 Lopinavir/ritonavir 13/75 Oseltamivir 8/75 Entecavir 1/75 Antibiotics 32/75 Corticosteroids 6/75	Umifenovir 33/75 Ribavirin 15/75 Lopinavir/ritonavir 12/75 Oseltamivir 9/75 Entecavir 1/75 Antibiotics 27/75 Corticosteroids 4/75

HCQ, hydroxychloroquine; PaO2, partial pressure of oxygen

[1] Cavalcanti 2020 - this was a three-arm trial, of which the third arm received HCQ + azithromycin.

[2] Chen 2020a - authors report that two participants received lopinavir/ritonavir, but it is unclear which study arms these participants were in. Whether or not any participants received corticosteroids or antibiotics is not reported.

[3] Chen 2020c - in addition to the above, authors report: "Both study group and comparison group received standard of care comprising supportive treatment for subjects with mild clinical COVID-19 symptoms and antimicrobial therapy for subjects presenting with moderate clinical COVID-19 symptoms. The treatment consisted of: (1) ceftriaxone 2 g daily for 7 days +/- azithromycin 500 mg on day 1 and 250 mg on days 2–5; or (2) levofloxacin 750 mg daily for 5 d; or (3) levofloxacin 500 mg daily; or (4) moxifloxacin 400 mg daily for 7–14 days for subjects allergic to ceftriaxone or azithromycin or according to physician discretion. Oseltamivir 75 mg b.i.d. will be administered for 5 days to subjects presenting with concomitant influenza A or B infection".

[4] Horby 2020 - authors presented the percentage of participants in each arm receiving dexamethasone or azithromycin. Data on antibiotics and other antivirals not reported. This trial was a platform trial with other arms testing tocilizumab, azithromycin, and dexamethasone, as well as convalescent plasma.

[5] Mitjà 2020a - the trial was originally designed to test HCQ with cobicistat-boosted darunavir, but this was modified during the trial as further information became available that cobicistat-boosted darunavir had no in vitro activity against SARS-CoV-2.

[6] Skipper 2020 - whether or not participants received antimicrobials or corticosteroids is not reported.

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Table 6. Adverse events for HCQ versus standard care without HCQ, or placebo, for treatment

Study	HCQ	No HCQ
Cavalcanti 2020	QTc prolongation (13/89) Arrhythmia (3/199) Bradycardia (1/199) Supraventricular tachycardia (2/199) Pneumothorax (1/199) Bloodstream infection (1/199) Itching (1/199) Nausea (9/199) Anaemia (14/199) Elevated ALT or AST (17/199) Elevated bilirubin (5/199) Hypoglycaemia (1/199) Leucopenia (3/199)	QTc prolongation (1/58) Arrhythmia (1/177) Bradycardia (1/177) Bronchospasm (1/177) Nausea (2/177) Vomiting (1/177) Anaemia (11/177) Elevated ALT or AST (6/177) Elevated bilirubin (2/177) Leucopenia (3/177)
Chen 2020a [1]	Transient elevated AST with anaemia (1/15) Diarrhoea (2/15) Fatigue (1/15)	Elevated AST (1/15) Elevated creatinine (1/15)
Chen 2020b	Headache (1/31) Rash (1/31)	
Mitjà 2020a	Gastrointestinal disorders (148/169) General disorders (30/169) Infections and infestations (9/169) Injury, poisoning, and procedural complications (1/169) Metabolic and nutrition disorders (2/169) Musculoskeletal and connective tissue disorders (1/169) Nervous system disorders (63/169) Psychiatric disorders (2/169) Renal and urinary disorders (1/169) Reproductive system and breast disorders (1/169) Respiratory, thoracic, and mediastinal disorders (2/169) Skin and subcutaneous tissue disorders (11/169) Vascular disorders (1/169)	Gastrointestinal disorders (7/184) General disorders (1/184) Infections and infestations (12/184) Metabolic and nutrition disorders (1/184) Nervous system disorders (3/184)
Skipper 2020 [2]	Upset stomach/nausea (66/212)	Upset stomach/nausea (26/211)

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Table 6. Adverse events for HCQ versus standard care without HCQ, or placebo, for treatment *(Continued)*

	Diarrhoea, other GI symptoms, vomiting (50/212) Neurologic (nervousness, irritability, dizziness, vertigo) (20/212) Skin reaction, rash (6/212) Ringing in ears (8/212) Allergic reaction, self-reported (5/212) Changes in vision (4/212) Warmth, hot flashes, night sweats (2/212) Headache (2/212)	Diarrhoea, other GI symptoms, vomiting (20/211) Neurologic (nervousness, irritability, dizziness, vertigo) (13/211) Skin reaction, rash (2/211) Ringing in ears (5/211) Changes in vision (5/211) Taste, dry mouth (1/211) Heart racing, anxiety, panic attack (1/211)
Tang 2020	Disease progression (1/70) Upper respiratory tract infection (1/70) Diarrhoea (7/70) Vomiting (2/70) Nausea (1/70) Abdominal discomfort (1/70) Blurred vision (1/70) Thirst (1/70) Sinus bradycardia (1/70) Hypertension (1/70) Orthostatic hypotension (1/70) Hypertriglyceridaemia (1/70) Decreased appetite (1/70) Fatigue (1/70) Dyspnoea (1/70) Flush (1/70) Kidney injury (1/70) Coagulation dysfunction (1/70) Decreased white blood cell (1/70) Increased ALT (1/70) Increased serum amylase (1/70) Decreased neutrophil count (1/70)	Abdominal bloating (1/80) Fever (1/80) Liver abnormality (1/80) Hepatic steatosis (1/80) Otitis externa (1/80) Increased serum amyloid A (1/80)

ALT: alanine aminotransferase; AST: aspartate transaminase; GI: gastrointestinal; HCQ: hydroxychloroquine

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[1]Authors of Chen 2020a comment that “among the test group the occurrence of adverse events in subjects with moderate to severe disease is not related to medication. All adverse reactions after drug withdrawal or symptomatic treatment disappeared”.
[2] Skipper 2020 - authors describe these adverse events as side effects reported at day 5.

APPENDICES

Appendix 1. Search strategies

Search strategy PubMed (MEDLINE)

#1	Search "Coronavirus"[Mesh]
#2	Search (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*) Field: Title/Abstract
#3	Search (((respiratory* AND (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") AND (Wuhan* or Hubei* or China* or Chinese* or Huanan*)). Field: Title/Abstract
#4	Search "severe acute respiratory syndrome*" Field: Title/Abstract
#5	Search ((outbreak* or wildlife* or pandemic* or epidemic*) AND (China* or Chinese* or Huanan*)) Field: Title/Abstract
#6	Search (corona* or corono*) AND (virus* or viral* or virinae*) Field: Title/Abstract
#7	Search (((((#1) OR #2) OR #3) OR #4) OR #6)
#8	Search chloroquin* Field: Title/Abstract
#9	Search Hydroxychloroquin* OR Oxychloroquin* Field: Title/Abstract
#10	Search ("Hydroxychloroquine"[Mesh]) OR "Chloroquine"[Mesh]
#11	Search Aralen or Plaquenil Field: Title/Abstract
#12	Search antimalaria* or anti-malaria* Field: Title/Abstract
#13	Search (((#8) OR #9) OR #10) OR #11OR #12
#14	Search (#13) AND #7

Database: Embase 1947-Present, updated daily

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1 coronavirus.mp. or Coronavirinae/

2 exp Coronavirinae/

3 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19

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(Continued)

or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).mp.

4 (respiratory* adj2 (symptom* or disease* or illness* or condition*)).mp.

5 ("seafood market*" or "food market*").mp.

6 4 or 5

7 (Wuhan* or Hubei* or China* or Chinese* or Huanan*).mp.

8 6 and 7

9 SARS coronavirus/ or severe acute respiratory syndrome/ or "severe acute respiratory syndrome*".mp.

10 ((outbreak* or wildlife* or pandemic* or epidemic*) adj2 (China* or Chinese* or Huanan*)).mp.

11 ((corona* or corono*) adj2 (virus* or viral* or virinae*)).mp.

12 1 or 2 or 3 or 8 or 9 or 10 or 11

13 hydroxychloroquine/ or chloroquine/ or chloroquin*.mp.

14 Oxychloroquin*.mp.

15 (Aralen or Plaquenil).mp.

16 (antimalaria* or anti-malaria*).mp.

17 antimalarial agent/ or antimalarial agent*.mp.

18 13 or 14 or 15 or 16 or 17

19 12 and 18

Search Name: Cochrane Central Register of Controlled Trials

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#1 MeSH descriptor: [Coronavirus] explode all trees

#2 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*)

#3 respiratory* AND (symptom* or disease* or illness* or condition*) AND (Wuhan* or Hubei* or China* or Chinese* or Huanan*)

#4 ("seafood market*" or "food market*") AND (Wuhan* or Hubei* or China* or Chinese* or Huanan*)

#5 "severe acute respiratory syndrome*"

#6 ((outbreak* or wildlife* or pandemic* or epidemic*) AND (China* or Chinese* or Huanan*))

#7 (corona* or corono*) AND (virus* or viral* or virinae*)

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 chloroquin*

#10 Hydroxychloroquin* OR Oxychloroquin*

#11 MeSH descriptor: [Chloroquine] explode all trees

#12 MeSH descriptor: [Hydroxychloroquine] explode all trees

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(Continued)

#13 Aralen or Plaquenil

#14 antimalaria* or anti-malaria*

#15 #9 or #10 or #11 or #12 or #13 or #14

#16 #8 and #15

HISTORY

Protocol first published: Issue 4, 2020
Review first published: Issue 2, 2021

Date	Event	Description
22 April 2020	Amended	Amended protocol title and updated Hannah Ryan affiliation details

CONTRIBUTIONS OF AUTHORS

BS and HR prepared initial drafts of Background and Methods; selected studies; assessed risk of bias; extracted data; synthesized data; and prepared initial drafts of results, 'Summary of findings' tables, discussion, and conclusions.

MC helped complete the Background and Methods; selected studies; assessed risk of bias; extracted data; synthesized data; and helped prepare and complete results, 'Summary of findings' tables, discussion, and conclusions.

TK helped complete the Background and Methods; assessed risk of bias; extracted data; and helped prepare and complete results, 'Summary of findings' tables, discussion, and conclusions.

TF helped complete the Background and Methods, results, 'Summary of findings' tables, discussion, and conclusions.

All authors read and approved the final version of the review.

DECLARATIONS OF INTEREST

BS is a Clinical Research Fellow for the National Institute for Health Research (NIHR) Global Health Research Group on Brain Infections at the University of Liverpool (No. 17/63/110) and in the NIHR Health Protection Research Unit on Emerging and Zoonotic Infections, and also works at the Royal Liverpool University Hospital, UK, and Christian Medical College, Vellore, India. He has no known conflicts of interest to declare with respect to chloroquine or hydroxychloroquine for the management of COVID-19.

HR is a Specialist Registrar in Clinical Pharmacology in Liverpool, and is employed as a full-time NHS clinician, and has no conflicts of interest to declare with respect to chloroquine or hydroxychloroquine for the management of COVID-19.

TK has no conflicts of interest to declare with respect to chloroquine or hydroxychloroquine for the management of COVID-19.

MC has no conflicts of interest to declare with respect to chloroquine or hydroxychloroquine for the management of COVID-19.

TF has no conflicts of interest to declare with respect to chloroquine or hydroxychloroquine for the management of COVID-19.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104

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- National Institute for Health Research (NIHR), UK

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- Medical Research Council (MRC), UK

  BS receives support from the MRC (project number MR/V033441/1). The views expressed in this review do not necessarily reflect UK government policy.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Regarding outcomes for Objective 1 - treatment of COVID-19, the review uses a different primary outcome measure for virological clearance: negative polymerase chain reaction (PCR) test at 14 days is used in place of time to negative PCR for SARS-CoV-2; the latter was not measured and reported consistently by trials. For serious adverse events, because most trials did not report attribution to hydroxychloroquine, and as a comparative outcome it may also be more relevant, total participants with any serious adverse events was used for analysis.

No subgroup analyses were conducted due to an inability to extract disaggregated data for the predefined subgroups.

Trials reported intention-to-treat as the primary analysis approach for the review's primary outcomes, so this was used for the primary meta-analyses within the review, rather than the planned available-case analysis. We performed a sensitivity analysis using modified intention-to-treat data, where trials reported this information.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [adverse effects] [*therapeutic use]; Antiviral Agents [adverse effects] [therapeutic use]; Bias; Cause of Death; Chloroquine [adverse effects] [*therapeutic use]; COVID-19 [*drug therapy] [epidemiology] [mortality] [*prevention & control]; COVID-19 Nucleic Acid Testing [statistics & numerical data]; Hydroxychloroquine [adverse effects] [*therapeutic use]; Pandemics; Prognosis; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; *SARS-CoV-2; Standard of Care; Treatment Outcome

MeSH check words

Adult; Aged; Humans; Middle Aged

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