Efficacy and Safety of Hydroxychloroquine and Chloroquine for Treating COVID-19: A Rapid Review

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Abstract

Background: Since its emergence, COVID-19 has affected more than one million people with over 100,000 deaths globally as of early April 2020. In this review, we evaluated the efficacy and safety of hydroxychloroquine and chloroquine on patients with COVID-19.

Methods: PubMed, CENTRAL, Google Scholar, Chinese Clinical Trial Registry and Trial Registers: ISRCTN; UMIN-CTR (Japan's Trial Register); and the WHO portal up were searched for the in vitro and in vivo studies of hydroxychloroquine and chloroquine.

Results: Moderate-certainty evidence from a single published RCT to-date showed that after a five-days treatment, patients on hydroxychloroquine may have shorter symptom duration compared to the control group, including fever (MD-1.0 day (95% CI -1.48, -0.52), cough (MD -1.1 day (95% CI -1.63, -0.57) and higher likelihood of having improved chest CT appearance (RR 1.47 (95% CI 1.02, 2.11), no clear differences was observed in the risk of progressing to severe illness and risk of adverse effects. A single non-randomized study showed marked decreased in the number with positive viral load at day 6, but due to several flaws in the study, the certainty of evidence for the outcome was very low.

Conclusion: Despite the evidence on possible effects of hydroxychloroquine and chloroquine, given the paucity of available evidence especially in relation to the number on-going RCTs, conclusion on the effectiveness and safety of hydroxychloroquine cannot yet be made.

Background

Since its emergence in the Hubei Province in Wuhan, China in December 2019, Coronavirus Disease (COVID–19) has spread to six continents, affected 1,610,909 people and resulted in approximately 99,690 death globally (1). COVID–19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV–2) that has genomic similarity with the virus that caused Severe Acute Respiratory Syndrome (SARS) in 2003 (2,3). Most people infected with the COVID–19 virus will experience respiratory illness with mild to moderate severity (4–6). The most vulnerable group of people such as the elderly and those with existing co-morbidities like cardiovascular disease, diabetes mellitus, chronic respiratory disease, and cancer have been identified to develop a more severe form of the disease (4,7,8). The virus is known to spread primarily through droplets of saliva or nasal discharge from the infected person when they cough or sneeze (9).

Researchers have been debating on the efficacy of hydroxychloroquine (HCQ) in inhibiting the SARS-CoV–2. Initial results from a placebo-controlled trial of HCQ for COVID–19 indicate that patients hospitalized with mild illness recovered more quickly with addition of the drug than with placebo at the start of a standard treatment (10). In contrast, a pilot study in China reported no difference in recovery rate among mild to moderate cases of COVID–19 when treated with HCQ (11). The efficacy of the drug in the treatment or prophylaxis of COVID–19 is still unknown. At present, there is still no treatment or vaccine for this disease (4).

HCQ is known to be a less toxic antimalarial drug compared to its analog chloroquine (CQ) because the addition of a hydroxyl group decreasing its toxicity while conserving its efficacy (12,13). It is also used as a disease-modifying anti-rheumatic drug to treat the acute and chronic rheumatoid arthritis, discoid and systemic lupus erythematosus (SLE), and juvenile idiopathic arthritis (JIA), owing to its immuno-modulatory effects (13,14). In the previous SARS outbreak in 2003, in vitro research suggested that the usage of CQ showed anti-SARS-CoV activity through virus/cell fusion

interference and post-entry spread of the virus (15). Hence, the hypothesis during this outbreak suggesting the possibility of HCQ as a potential pharmacological agent for the treatment of COVID–19 infection.

Since the COVID–19 was declared as a global pandemic, scientists and pharmacological companies are desperate to find the effective treatment(s). The ill-informed and non-evident based interpretation of the efficacy of the HCQ/CQ have great potential in causing serious harm to the public. There are no clinical evidence to support the use of HCQ/CQ as a treatment or prophylaxis for SARS-CoV–2 infection. Therefore, this review aims to determine the efficacy and safety of HCQ and CQ given as a single drug or in combination with standard care with or without any other antimicrobial agent.

Methods

We searched the PubMed, CENTRAL, Google Scholar, Chinese clinical trial registry, and trial registers: ISRCTN; UMIN-CTR (Japan's Trial Register); the WHO portal up to 9th April 2020 using the search terms *chloroquine, hydroxychloroquine, coronavirus, SARS-Cov–2, 2019-NCov, and COVID–19. We screened the titles and abstracts, and included in vitro and in vivo studies of CQ/HCQ for the treatment of SARS-CoV–2. The criteria for considering studies to be included in this review is listed in Table 1.

Table 1: Criteria for considering studies to be included in this review.

Criteria	Description
Types of studies	We included one RCT and one non-randomized comparative study and in vitro studies.
Types of participants	Patients with confirmed case of COVID- 19.
Types of interventions	HCQ/CQ in single or in combination with other standard therapy at any dosage stated by study authors
Comparison	Conventional standard therapy
Types of outcome measures	Primary outcomes 1. Efficacy of HCQ/CQ in patients with COVID-19 measured in terms of virological clearance over time by the real-time reverse transcriptase polymerase chain reaction (RT-PCR) or changes in time-to-clinical recovery (TTCR) which is defined by study author (10) 2. Reduction of symptoms such of cough, phlegm, reduction of temperature, changes in chest x ray or oxygen saturation Secondary outcomes 1. Safety of HCQ is measured by the absence of adverse events 2. Adverse events such as cardio, renal, liver and visual toxicities as mentioned by the study authors.

Footnotes: RCT – randomized-controlled trial; HCQ – hydroxychloroquine; CQ – chloroquine; RT-PCR – reverse transcriptase polymerase chain reaction; TTCR – time to clinical recovery

Data collection and analysis

Selection of studies

The standard Cochrane methods were employed, as described in the Cochrane Handbook for Systematic Reviews of Interventions (16). Two review authors (NAM and CJ) independently screened for potentially eligible studies by inspecting the titles and abstracts to generate a shortlist. Two review authors (CJ and NSMD) then independently inspected the abstracts and/or full texts of these shortlisted studies further to determine final eligibility, using the predefined inclusion and exclusion criteria. We resolved any disagreement with the help of another review author (TA) as a referral. We included published studies available in full-text article.

Data extraction and management

Two review authors (NSMD and MFB) independently extracted all data from each included study using a dedicated data collection form. We collected study characteristics, including study design, setting, country, participants, interventions, comparators, outcomes and any other information considered relevant according to Cochrane Handbook for Systematic Reviews of Interventions (16). We resolved potential discrepancies through discussion and involved another review author (NML) if necessary.

Assessment of risk of bias in included studies

Two review authors (NAM and NML) independently assessed one included study for risk of bias (ROB) according to the following seven criteria, in accordance with the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (16).

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We made a judgment of low, high, or unclear ROB, with justifications based on the information obtained from the study (10). We assessed the ROB and presented in a Risk of bias' table for one study (10). We used ROBINS-I risk of bias tool to assess the risk of bias for non-randomized comparative study (17). We included the following outcomes in the 'Summary of Findings' table:

- Duration of fever resolution

- Duration of cough resolution
- Number of patients who progressed to severe illness
- Number of patients with adverse effects
- Number of patients with improved chest CT appearance
- Number of patients with negative viral load on day 6

Whenever we identified an issue in each of the five GRADE criteria that was considered a serious risk to influence the outcome estimate, we downgraded the quality of evidence by one level, and when we considered the issue to be very serious, we downgraded the quality of evidence by two levels (18). When we decided to downgrade the quality of evidence from the default high quality, we justified our decision and described the level of downgrading in the footnotes of the table. We constructed the 'Summary of Findings' table using an internet-based version of GRADEpro software (19) according to the methods and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (16).

Results

Description of studies

From the initial search through PubMed (2147), CENTRAL (0) and Google Scholar (300), 2450 records were identified, with 163 records remaining after removing duplicates. Of these, eight articles appeared to be relevant after we inspected the titles. We evaluated these eight articles further by reading the abstracts, excluding three records in the process. We assessed the full-texts of the remaining three articles to determine final eligibility, and included five articles (three in vitro, two in vivo) in our final analyses. We also identified 43 relevant on-going studies with no results posted in the trial registry website (International Clinical Trials Registry platform ICTRP = 22 and Chinese Clinical Trial Registry ChiCTR = 21). The PRISMA flow chart of the studies selection from the initial search to the result is shown in Figure 1. We described all the characteristics of included studies in Table 2 and 3. The ROB table for RCT is presented in Table 4, and the non-randomized comparative study risk of bias is presented in Supplementary Table 1. The Summary of Findings is listed in the Supplementary Table 2.

Table 2: Characteristics of in vitro studies included in this review.

Footnotes: HCQ – hydroxychloroquine; CQ – chloroquine; CC50 – 50% cytotoxic concentration; µM – micromolar; EC50 – 50% maximal effective concentration; MOI - multiplicity of infection

Table 3: Characteristics of in vivo studies included in this review.

First author, Year	Study title	Place of study	Study design	Type of Drugs	Key finding
Liu et al., 2020 (20)	Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro	China	Experimental Study In-Vitro	Hydroxychloroquine (HCQ) and Chloroquine (CQ)	• 50% cytotoxic concentration (CC50) values of CQ and HCQ were 273.20 and 249.50 µM, respectively • 50% maximal effective concentration (EC50) was lower for CQ (2.71, 3.81, 7.14, and 7.36 µM) as compared to HCQ (4.51, 4.06, 17.31, and 12.96 µM) irrespective of the multiplicity of infection (MOI).
Yao et al., 2020 (21)	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)	China	Experimental Study In-Vitro	Hydroxychloroquine	• This study showed that both CQ and HCQ have good antiviral activity. • CQ and HCQ showed a reduction in the viral replication proportionate with its concentration. • The EC50 values for CQ were 23.90 and 5.47 µM at 24 and 48 hours, respectively. • EC50 values for HCQ were 6.14 and 0.72 µM at 24 and 48 hours, respectively, MOI = 0.01.
Wang et al., 2020 (22)	Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro	China	Experimental Study In-Vitro	Remdesivir and chloroquine	• This study showed that remdesivir and CQ are highly effective in the control of SARS -CoV-2

	infection in vitro. • CQ (EC50 = 1.13 μM; CC50 > 100 μM, MOI = 0.05) effectively blocked virus infection at low-micromolar concentration.

First author, Year	Study title/ Place of Study	Study Design	Intervention/ Comparison	Method	Sample size, n	Key finding
Gautret et al., 2020 (17)	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial (France)	Open-label non-randomized clinical trial	HCQ and Azithromycin / standard care	A total of 26 patients received HCQ and 16 were control patients. Six HCQ-treated patients were lost to follow-up during the study. A total of 26 patients were assigned to the treatment group, and received HCQ 200mg three times a day for ten days. The control group received usual care. Among HCQ treated patients, six patients received azithromycin (500mg on day 1 followed by 250mg per day, the next four days) to prevent	36	• HCQ-treated patients were older than control patients (51.2 years vs. 37.3 years). • No significant difference was observed between HCQ-treated patients and control patients with regard to gender, clinical status and duration of symptoms prior to starting the study. • The proportion of patients that had negative RT-PCR results in nasopharyngeal samples significantly differed between treated patients and controls at days 3, 4, 5 and 6. • Day 6: 70% of HCQ treated patients were virologically-cured comparing with 12.5% in the control group (p= 0.001). • Day 6: 100% of patients treated with HCQ and azithromycin combination were virologically-cured comparing with 57.1% in patients treated with HCQ only, and 12.5% in the control group (p<0.001).

				bacterial super-infection.	• Drug effect was significantly higher in patients with symptoms of URTI and LRTI, as compared to asymptomatic patients with $p<0.05$ (data not shown). • One patient who was still RT-PCR-positive at day 6 under HCQ-treatment only, received azithromycin in addition to HCQ at day 8 inclusion and cured her infection at day 9 post-infection. • In contrast, one of the patients under HCQ and azithromycin combination who tested negative at day 6 was tested positive at low titer at day 8.
Chen et al., 2020 (10)	Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial	Randomized clinical trial Randomization was performed through a computer-generated list stratified by site	HCQ vs. standard care	HCQ treatment group received additional oral HCQ (HCQ sulfate tablets) 400 mg/d (200 mg/bid) between days 1 and 5 along with standard care (31) and patients in control group (31) received standard care i.e. oxygen therapy,	62 • The study showed a significant difference in Time-To-Clinical-Recovery (TTRC) between the two groups. • For fever, 17 patients (control group) and 22 patients (HCQ treatment group) had a fever in day 0. Compared with the control group [3.2 (1.3) days], the body temperature recovery time was significantly shortened in the HCQ-treatment group [2.2 (0.4) days].

		antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids	• For cough, 15 patients (control group) and 22 patients (HCQ-treatment group) had a cough in day 0. The cough remission time was significantly reduced in the HCQ-treatment group. • Notably, a total of 4 of the 62 patients progressed to severe illness, all of which occurred in the control group not receiving HCQ-treatment. • For adverse effects, there were two patients with mild adverse reactions in the HCQ-treatment group, one patient developed a rash, and one patient experienced a headache, none severe side effects appeared among them. • They compared and analyzed the chest CT of patients on day 0 and day 6 to see the effect of HCQ on pneumonia. • In this study, pneumonia was improved in 67.7% (42/62) of patients, with 29.0% moderately absorbed and 38.7% significantly improved. • Patients in the HCQ-treatment group have improved pneumonia (80.6%, 25 of

							31) compared with the control group (54.8%, 17 of 31). Besides, 61.3% of patients in the HCQ-treatment group had a significant pneumonia absorption.

Footnotes: HCQ - hydroxychloroquine; PCR – polymerase chain reaction; URTI – upper respiratory tract infection; LRTI – lower respiratory tract infection; TTRC – time to clinical recovery; CT – computerized tomography

Measurement risk of bias

1. Chen et al. (2020)(10)

Study design: Randomized-controlled trial

Table 4: The description for measurement risk of bias for in vivo study by Chen et al. (2020).

Item	Risk	Remarks
ndom quence neration	Low	Methods, “Treatments were assigned after confirming the correctness of the admission criteria.”
ocation ncealment	Unclear	Insufficient information provided on who performed the sequence generation and how allocation was implemented to enable an assessment of the relationship between sequence generation and allocation.
nding articipants d rsonnel)	Low	Methods, “Neither the research performers nor the patients were aware of the treatment assignments.”
nding utcome sessor)	Low	Methods, “Neither the research performers nor the patients were aware of the treatment assignments.”
complete tcome ta	Low	Results, “62 patients were identified as having COVID-19 and enrolled in this study, none quit”.
lective tcome porting	Low	Major clinical outcomes pre-specified in the methods, including adverse effects were reported insufficient detail in the results.
her bias	Low	None identified.

2. Gautret et al. (2020) (17)

Study design: Non-randomized comparative study

Tool: ROBINS-I (23) (Supplementary Table 1)

No clinical outcomes reported in this paper (to be reported in a separate paper).

Comment on ROB:

1. Non-randomized trial

- Those who refused HCQ were allocated to the control group: in general, patients who refused treatment tend to be prognostically worse as a group, raising concerns on ROB. The age difference between the two groups

does not seem to pose a major prognostic imbalance, and other major characteristics appear comparable between the two groups. However, the authors have only taken into account of the known prognostic factors in reporting these characteristics.

- The rest of control group composed of patients from other centers, for whom care regimen, in particular, and co-intervention might be different, and these were not elaborated in the paper. Viral testing, the major outcome reported, were done differently between the two groups, as in the control patients, patients were tested every alternate day's vs. HCQ patients for whom testing was done every day. In control group patients, if the positive viral results was missed on the day of reporting, results were carried forward from the previous day. This is another evidence of performance bias being present.
- The intervention group enrolled 26 patients, while the control group enrolled 16. It was unclear the reason for discrepancy on the number of participants between intervention and the control group. It was unlikely to be due to a lack of relevant patients. Was there a statistical consideration to make the result appealing?
- Stopping before target participants' number: the trial was stopped when 36 out of 42 target participants were reached. In general, stopping trial early for benefit tends to make the trial results more exaggerated than stopping on time. This raises the following query: since COVID patients were rapidly available consecutively, it would not have taken long to add another 6 patients to complete the trial, why stopped at 36? Could it be possible that patients 37–42 on HCQ were actually available, but adding them would have made the results less drastically favoring HCQ?
- Loss of follow-up: 6 patients in HCQ group were lost to follow up, and their data were not included in the report. 4 out of the 6 were positive in their last reading. Including the results of the four from their last readings carried forward, or even taking a plausible proportion of these patients to be assumed as positive on day 6 (a convenient way is to assume 50% positive: i.e. 2 positive cases on day 6, would decrease the difference in the proportion with positive viral load in between groups).

Discussion

Through a comprehensive search strategy, we identified three in vitro studies (20–22) from the search strategy. Generally, two studies (20,21) report that the HCQ is more potent to SARS-CoV–2 than CQ. However, the long term usage of HCQ in patients might lead to toxicity. In another study (22), it is reported that CQ and remdesivir are more effective on SARS-CoV–2. HCQ is not included in this study. From our analysis and certainty of evidence rating, HCQ or possibly CQ may have given moderate effects on SARS-COV–2.

Besides the in vitro studies, we identified two in vivo studies that matched our selection criteria in terms of population, intervention, comparison and outcomes. We believe the study gathered in this review represented the best available evidence to answer the question that we posed in conducting this review. One in vivo study was a randomized-controlled trial which compared the use of HCQ and standard therapy in 62 patients (10). Another in vivo study was non-randomized comparative trial in which HCQ and azithromycin was compared with standard care among 36 patients (17). Overall, the use of HCQ showed reductions in the symptoms of COVID–19 and laboratory findings, measured primarily as improvement of symptoms such as fever and cough. However, both studies showed low quality of evidence. The sample size was relatively small as compared to the number of COVID–19 patients in both countries.

Despite our broad search strategies, we might have missed the relevant articles that examined HCQ due to the widely variable description of COVID–19 and corresponding interventions. There are 43 on-going trials that are yet to be included in our analyses, and with the large number of studies and participants in most outcomes, the inclusion of these studies might change the overall findings.

There is a concern that HCQ and CQ might have adverse effects on COVID–19 patients (24). The author questioned the in vivo study by Gautret et al. (2020) (17) that has small sample size and methodology limitations. The author also mentioned that the use of HCQ or CQ in combination with azithromycin might predispose the patients to life-threatening arrhythmias, hypoglycemia, neuropsychiatric effects, idiosyncratic hypersensitivity reactions, and drug–drug interactions. Besides that, HCQ and CQ overdose can lead to extreme toxicity. We agree with the author's view on small sample and methodology limitation as what we have mentioned earlier.

Conclusion

There is some evidence from one RCT and one non-randomized comparative study that HCQ appears to modestly reduce SARS-CoV–2 activity, but there is so far no clear evidence that HCQ affects other outcomes as what have been mentioned by Juurlink (2020) (24) with no data on adverse effects and animal-model outcomes. However, the certainty of the estimates for all outcomes (or the quality of evidence) were very low-to-moderate, which means there is a clear possibility that the overall findings may change with further research.

In view of the very low-to-moderate certainty of evidence presented in this review, more well-conducted RCTs are needed. Future RCTs should adheres to rigorous standards with clear documentation, to provide improvement in the overall certainty of evidence. There is a lack of high-quality evidence that supports the efficacy and safety of HCQ and CQ for treatment of COVID–19. The available evidence precluded any clear conclusion to inform medical practice.

List Of Abbreviations

COVID–19: Novel Coronavirus Disease 2019

SARS-CoV–2: Severe acute respiratory syndrome coronavirus 2

SARS: Severe Acute Respiratory Syndrome

HCQ: Hydroxychloroquine

CQ: Chloroquine

RT-PCR: Reverse-transcriptase polymerase chain reaction

MOI: Multiplicity of infection

RR: Relative risk

RCT: Randomized-controlled trial

ROBINS-I: Risk of bias tool to assess non-randomized studies of interventions

URTI: Upper respiratory tract infection

LRTI: Lower respiratory tract infection

SLE: Systemic lupus erythemathosus

JIA: Juvenile idiopathic arthritis

ISRCTN: International standard randomized controlled trial number

UMIN-CTR: University hospital medical information network clinical trial registry

CENTRAL: Cochrane Controlled Register of Trials

WHO: World Health Organization

TTCR: Time to clinical recovery

ROB: Risk of bias

ICTRP: International Clinical Trials Registry Platform

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

EC50: 50% maximal effective concentration

CC50: 50% cytotoxic concentration

μM: Micromolar

CT: Computerized tomography

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NAM conceive the idea and performed the analysis and wrote the draft manuscript and contributed to the final manuscript. NML performed the analysis and contributed to the final manuscript. CJ developed and discussed the search strategies and contributed to the final manuscript. NSMD discussed the results and contributed to the final manuscript. MFB developed the theory and wrote the draft manuscript, discussed the results and contributed to the

final manuscript. TA verified the results, supervised the findings of this work and contributed to the final manuscript. All authors read and approved the manuscript.

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Figures

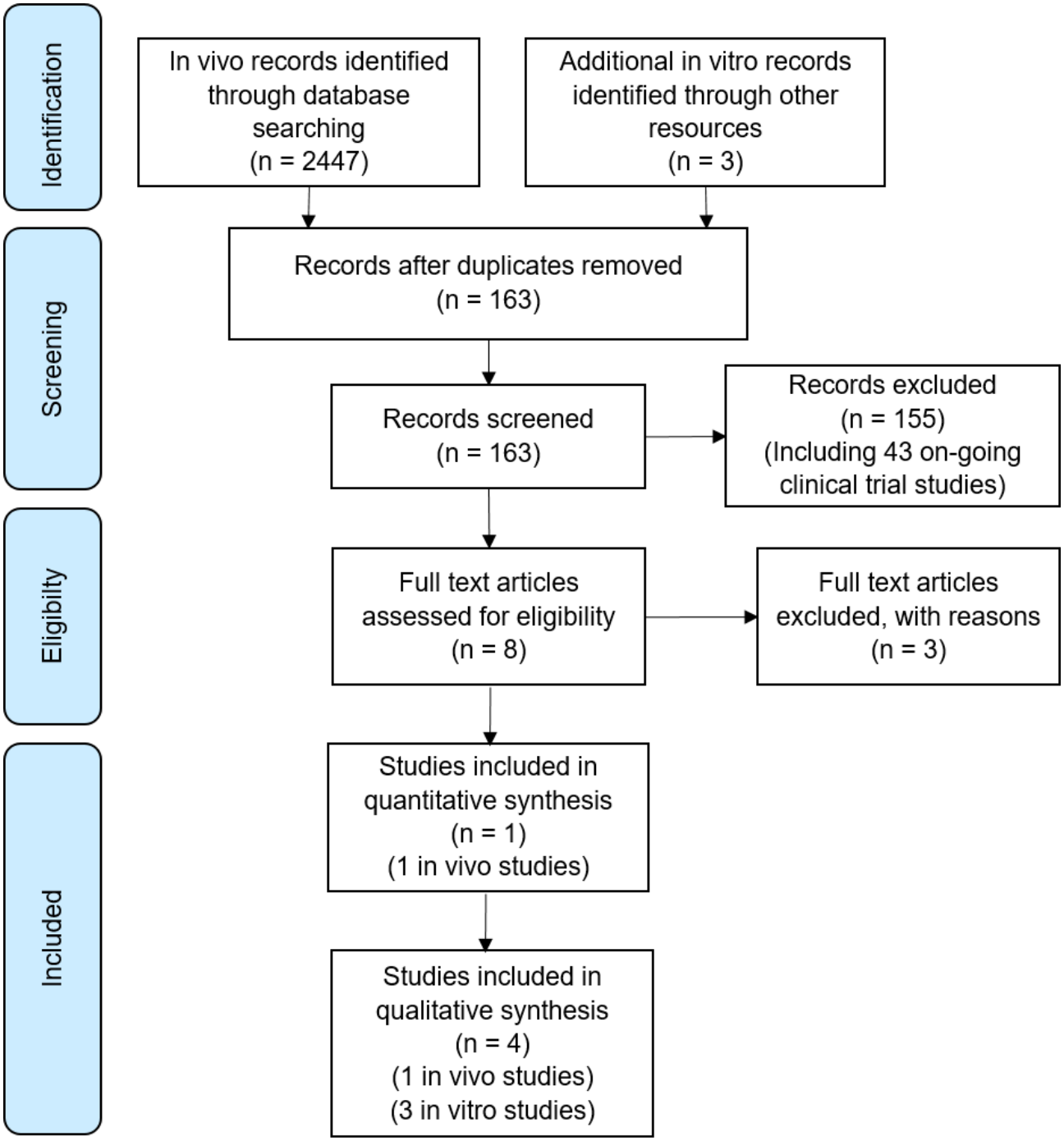

Figure 1

The PRISMA flow chart for in vivo and in vitro study of hydroxychloroquine and chloroquine in COVID-19.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable3.docx
- SupplementaryTable1.docx
- SupplementaryFigure1.docx

- SupplementaryTable2.docx