Chloroquine and hydroxychloroquine for prevention of COVID# 19: evidence review of clinical benefits and harm

South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: CHLOROQUINE AND HYDROXYCHLOROQUINE FOR PREVENTION OF COVID-19: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

Date: 18 JUNE 2020

Key findings

- We conducted a rapid review of available published clinical evidence regarding use of chloroquine or hydroxychloroquine for prevention and post-exposure prophylaxis of COVID-19.
- After searching widely on 10 June 2020, we found one clinical trial comparing hydroxychloroquine to placebo for post-exposure prophylaxis of COVID-19. The trial took place in North America, including 821 participants and was stopped early when no benefit was found. They found no difference in new COVID-19 infections (combined laboratory confirmed and clinically diagnosed), and there were probably 2-fold greater number of participants reporting adverse events. There were no serious adverse events.
- In people exposed to COVID-19, we recommend not using hydroxychloroquine for post-exposure prophylaxis (conditional recommendation).

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation		**X**			

Recommendation: Based on this evidence review the NEMLC Subcommittee does not recommend hydroxychloroquine/chloroquine for the prevention of COVID-19, unless there is new evidence of efficacy that shows benefit.
Rationale: Evidence from one trial of HCQ compared to placebo for prevention of COVID-19 found no difference in the incidence of presumed new infections (low certainty evidence) but a 2-fold greater number of participants complaining of adverse events (moderate certainty evidence). The trial was stopped early for futility according to preplanned stopping rules.
Level of Evidence: Disease oriented RCT of low-moderate certainty evidence

(Refer to Appendix 1 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

Strategies to minimize the transmission and acquisition of COVID-19 have been instituted in most countries globally, including physical distancing, hand hygiene practices and use of masks by communities. Despite this, COVID-19 cases continue to rise, placing health systems under extreme pressure to provide adequate care for those who become ill and require care in health facilities. Prevention of transmission of COVID-19 is one strategy to reduce case load, illness and strain on the health system.

In addition to the non-pharmaceutical approaches to prevent transmission, medicines may offer another strategy to prevent infections. Globally, the research community is trying to find an effective and safe medicine to use for prophylaxis or for use following exposure to a possible case of COVID-19 (post-exposure prophylaxis). To date there are no globally accepted recommended medicines to prevent transmission, but several are being explored. Chloroquine (CQ) and hydroxychloroquine (HCQ) are amongst the medicines receiving substantial public attention and interest.

CQ and HCQ are 4-aminoquinoline compounds, derivatives of quinine, and have been used successfully for prevention and treatment of malaria for decades until resistance arose. They are currently used in South Africa for management of rheumatological diseases (SAMF, 13th ed., 2020). Following the COVID-19 outbreak, several in vitro studies have reported that CQ or HCQ inhibit SARS-CoV-2 activity (Wang 2020, Liu 2020), suggesting a potential role of CQ and HCQ for preventing infection.

Both the efficacy and safety of a new medical intervention are important to consider. Medicines for preventing conditions are given to those who do not have the illness and may be otherwise well, therefore the benefits should clearly outweigh the harms. CQ and HCQ have been in use for decades and have a well-known safety profile outside of use in COVID-19 with several common adverse effects (gastrointestinal effects, skin rash, headache, vertigo, and blurred vision at higher doses) and rare effects (ototoxicity, blood dyscrasias, cardiovascular, such as QT interval prolongation and neuropsychiatric effects) (SAMF, 13th ed., 2020). However, there have been reports from studies in COVID-19 patients that suggest important safety concerns that require consideration, particularly for cardiovascular events due to QT prolongation.

A systematic review of CQ and HCQ for COVID-19 treatment and prophylaxis reported safety outcomes of all its included studies (Hernandez 2020). Although for most minor adverse events, there do not seem to be differences in events, there have been several signals about QTc Interval Prolongation or arrhythmias. The review reported that one cohort study evaluating HCQ (Mahe'vas 2020) and another assessing CQ (Borba 2020a, Borba 2020b) versus control found increases in QTc interval prolongation to 500 ms or greater. HCQ increased the QTc interval more than 60 ms from baseline, whereas chloroquine increased the number of patients experiencing ventricular tachycardia versus control. Another cohort study assessed the effect of HCQ with and without azithromycin on the QTc interval in 90 patients (mean age, 60 years; 51% male) (Mercuro 2020). Slightly more patients receiving HCQ plus azithromycin had a QTc interval of 500 ms or greater (11 of 53 [20.8%] vs. 7 of 37 [18.9%]; mean difference, 1.8% [95% CI, –14.9% to 18.5%]), and more patients had a QTc interval increase of 60 ms or more from baseline (7 of 53 [13.2 %] vs. 3 of 37 [8.1%]; mean difference, 5.1% (CI, –7.6% to 17.8%]) versus hydroxytoluene alone. One patient receiving HCQ and azithromycin had a QTc interval of 499 ms and developed torsade de pointes' (Hernandez 2020). Although the evidence from controlled studies remains underpowered, it is important that safety and drug interactions of CQ and HCQ use is closely monitored in COVID-19 studies. This is particularly because of the higher doses and co-medications, some with known drug interactions that were used in these studies compared to typical use for rheumatological or malaria indications.

This rapid review aimed to evaluate the available research evidence for the efficacy and safety of CQ and HCQ for prophylaxis and post-exposure prophylaxis of COVID-19 infections.

RESEARCH QUESTION: Should chloroquine or hydroxychloroquine be used for prevention or post-exposure prophylaxis for COVID-19 compared to no intervention or an alternative intervention?

METHODS

We conducted a rapid review of the evidence including comprehensive searching three electronic databases - Epistemonikos, Cochrane Library COVID-19 study register and the COVID-nma.com Living review database - on 10 June 2020. These databases systematically search the following electronic databases: PubMed, Embase, MedRxiv, WHO's ICTRP and clinicaltrials.gov, amongst others. The search strategy is shown in Appendix 2.

We screened retrieved records against the eligibility criteria; we first screened the titles and abstracts in duplicate and proceeded to screen the full texts in duplicate. One reviewer (SD) extracted the review findings into the characteristics of included studies table which was checked by the other reviewer (TK) (Table 1). The risk of bias of the included trial was assessed by one reviewer using Cochrane's Risk of Bias Tool and discussed with a second reviewer. SD and TK used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to for grading evidence, presenting results in a Summary of Findings table (Guyatt 2008). All reviewers drafted the report before sending for further evaluation to the NEMLC COVID-19 subcommittee.

Eligibility criteria for review

Population: People who are at risk of SARS-CoV-2 exposure or have had a possible exposure, as defined by study authors. No restriction on age or occupational setting.

Intervention: Chloroquine (CQ) or hydroxychloroquine (HCQ) given by any route of administration, any dose, used alone or in combination with other pharmacological agents, for prophylaxis or post-exposure prophylaxis of COVID-19 infection. No restriction on timing of dosing in relation to time of potential exposure/s to SARS-CoV-2.

Comparators: no comparator, or an active comparator.

Outcomes:

Efficacy outcomes:

- Development of laboratory confirmed COVID-19
- Disease severity of participants who develop COVID-19, as defined by study investigators

Safety outcomes

- Adverse reactions
- Adverse events

Study designs: Systematic reviews of controlled studies. In the absence of an up-to-date, good quality review, we sought the following studies in this order: randomized controlled trials and other comparative studies.

RESULTS

Results of the search

We identified 949 records from the search on 10 June 2020, and after removing 421 duplicates we included 528 records for screening in duplicate. We excluded 437 studies which were irrelevant and then screened 91 full texts in duplicate. Seven studies were excluded as they were: the wrong study design (n = 4), the wrong intervention (n = 1), the wrong patient population (n = 1), and one was a review on planned studies in clinical trial registries. Eighty-one were ongoing studies from clinical trials registers. Two systematic reviews (Shah 2020 and Hernandez 2020) and one clinical trial (Boulware 2020) were included (Figure 1). Our search identified 72 planned or ongoing studies registered in clinical trials registers for CQ or HCQ overall, with 22 specific to CQ or HCQ prophylaxis (from the www.covid-nma.com 9 June 2020) (Appendix 3).

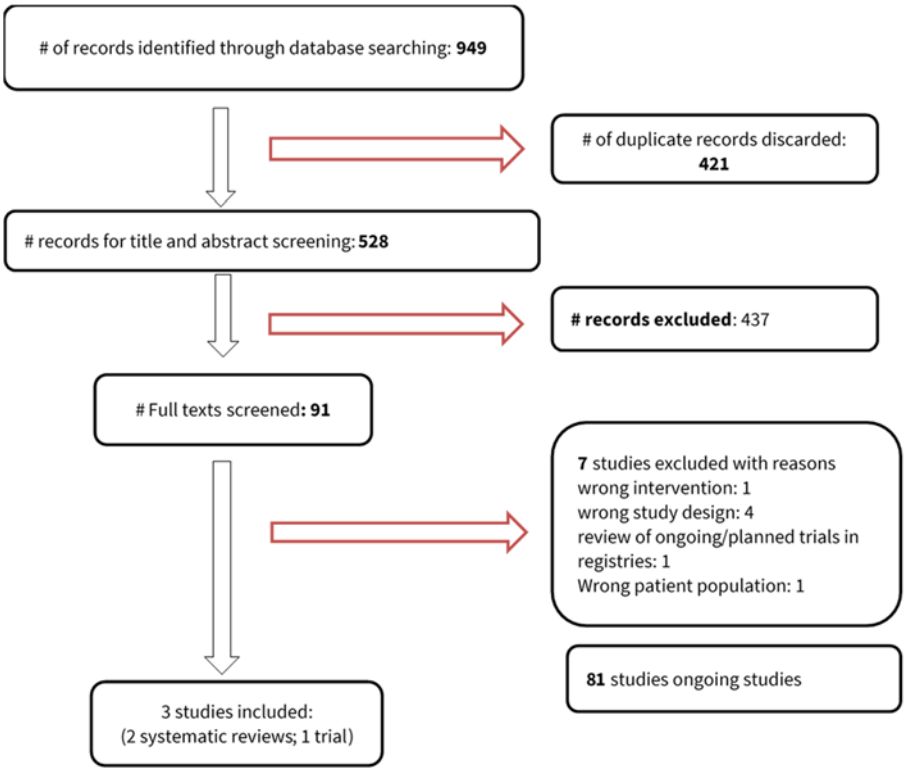

Figure 1. *PRISMA flowchart of study selection process*

Description of included studies

We identified two systematic reviews, but these did not include any studies with relevant data to address our questions (Shah 2020 and Hernandez 2020). We included one randomized controlled trial (Boulware 2020) (detailed characteristics of the trial are reported in Table 1). The trial was conducted in the U.S.A and Canada, randomised 821 participants without COVID-19 who had an exposure to someone with COVID-19 to either HCQ or placebo (folate tablets). The Data Safety Monitoring Board decided to terminate the trial early for futility, before reaching the planned sample size, according to planned stopping rules.

Effects of interventions

Results of the single included trial (Boulware 2020) on the outcomes of interest are summarized in the Summary of Findings table (Table 2) and are presented below.

Development of laboratory confirmed COVID-19: There were 11/414 laboratory confirmed cases of COVID-19 in the HCQ arm compared to 9/407 in the placebo arm. The trialists also reported on a composite of laboratory and clinically diagnosed COVID-19 infections (due to limited access to PCR testing). Figure 2 shows the composite results. Evidence from the trial indicates that there is probably no difference in the number of new infections between HCQ and placebo (Risk Ratio RR 0.83 [95% CI 0.58, 1.18], low certainty evidence). The evidence was rated down for imprecision and indirectness, due to inclusion of non-laboratory informed cases.

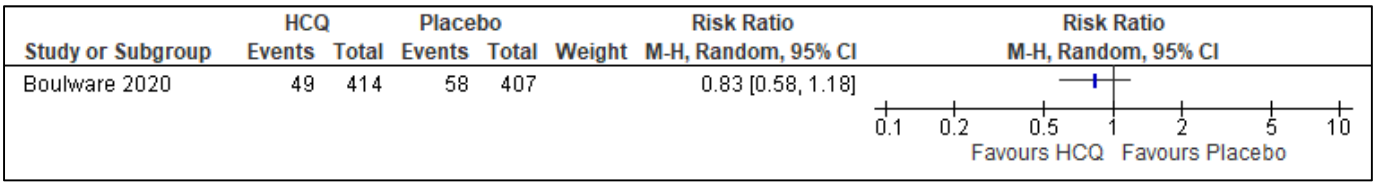

Figure 2. *Forest plot for outcome: Development of laboratory or clinically confirmed COVID-19*

Disease severity of participants who develop COVID-19, as defined by study investigators: One participant in each group was hospitalised. Symptom severity was reported as median (interquartile range - IQR) on a scale of 0 – 10, with 10 indicating greatest severity. The median severity score was 2.8 (IQR 1.6 to 5.0) in those receiving HCQ and 2.7 (IQR 1.4 to 4.8) in those receiving placebo (p = 0.34).

Adverse reactions: this was not reported in the included trial.

Adverse events: The actual number of adverse events was not available from the study report. The authors published the number of participants who reported adverse events. There is moderate certainty evidence that there is probably a two-fold greater number of participants who experience adverse events in the HCQ group compared to placebo (Figure 3). The evidence was rated down due to imprecision as this is a single study with a small sample and few events.

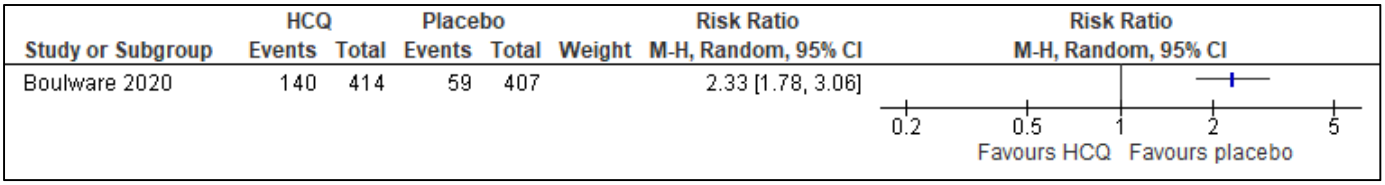

Figure 3. *Forest plot for outcome: Number of participants who experienced adverse events (not total number of events per group)*

CONCLUSION

Evidence from one trial of HCQ compared to placebo for prevention of COVID-19 found no difference in the incidence of presumed new infections (low certainty evidence) but a 2-fold greater number of participants complaining of adverse events (moderate certainty evidence). The trial was stopped early for futility according to preplanned stopping rules.

Reviewers: Tamara Kredo, Solange Durao, Marc Blockman

Declaration of interests: None to declare in respect of this topic. SD and TK (Cochrane South Africa, South African Medical Research Council, SA GRADE Network), MB (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town).

REFERENCES

1. South African Medical Formulary 13th Edition, 2020.
2. 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]
3. 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]
4. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review. Annals of internal medicine. 2020.[DOI: 10.7326/M20-2496]
5. Mahe´vas M, Tran VT, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv. 14 April 2020. doi:10.1101/2020.04.10.20060699
6. Borba MG, Val FdA, Sampaio VS, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). medRxiv. 16 April 2020. doi:10.1101/2020.04.07.20056424
7. Borba MGS, Val FFA, Sampaio VS, et al; CloroCovid-19 Team. 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 Netw Open. 2020;3:e208857. PMID: 32339248] doi:10.1001/jamanetworkopen.2020.8857
8. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020. [PMID: 32356863] doi:10.1001/jamacardio.2020.1834
9. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
10. 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). *Int J Rheum Dis*. 2020; 23: 613– 619. [https://doi.org/10.1111/1756-185X.13842]

11. 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. [DOI: 10.1056/NEJMoa2016638]

Table 1. Characteristics of included comparative studies

Citation	Study design	Population	Intervention	Main findings	Risk of Bias
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.	Randomised clinical trial	Setting: U.S.A and Canada Participants were treated at home (received treatment via courier). n = 414 Hydroxychloroquine n = 407 placebo group Eligibility: "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" <3 days after presumptive-case exposure [17 March] <4 days after confirmed-case exposure [23 March] Exposure: <6ft, >10 mins: - No mask & no eye protection = high-risk - Mask but no eye protection = moderate-risk Exclusion criteria: <18 years old, hospitalised, symptoms of COVID-19, PCR positive for SARS-CoV-2, in April 2020, this extended to exclude heart disease, family history of QT prolongation, potential interacting medicines	Hydroxychloroquine 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). Control: Placebo (Folate tablets)	Main outcomes reported: Incidence COVID-19 lab or clinically diagnosed Secondary outcomes: •Hospitalization for Covid-19 or death •PCR-confirmed SARS-CoV-2 infection •Covid-19 symptoms •Discontinuation of the trial intervention - 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: direct questioning for common side effects along with open-ended free text. See table 2 with all results reported. Other outcomes: The median number of symptoms was 4 (interquartile range, 2 to 5) among participants with Covid-19. The most frequent symptoms were cough (44.9% of the 107 participants with Covid-19), fever (34.6%), shortness of breath (18.7%), fatigue (49.5%), sore throat (40.2%), myalgia (37.4%), and anosmia (23.4%). Full adherence to the trial intervention differed according to trial group, with 75.4% of participants in the hydroxychloroquine group (312 of 414) and 82.6% of those in the placebo group (336 of 407) having taken all 19 prescribed tablets over a period of 5 days (P=0.01).	Low overall risk of bias (Cochrane Risk of Bias tool). However, the trial did terminate early due to calculated futility of the intervention.

Table 2. Summary of Findings table

Chloroquine (CQ) or hydroxychloroquine (HCQ) compared to no comparator or an active comparator for COVID-19 prevention						
Patient or population: individuals exposed to COVID-19 positive cases **Setting**: U.S.A, Canada, recruitment via social media/traditional media outreach with self-enrollment through REDCap system **Intervention**: Hydroxychloroquine (HCQ) **Comparison**: Placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**Risk difference with Chloroquine (CQ) or hydroxychloroquine (HCQ)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with no comparator or an active comparator	**Risk with Chloroquine (CQ) or hydroxychloroquine (HCQ)**				
Development of laboratory or clinically confirmed COVID-19 assessed with: PCR follow up: 14 days	143 per 1,000	**118 per 1,000** (83 to 168)	**RR 0.83** (0.58 to 1.18)	**24 fewer per 1,000** (60 fewer to 26 more)	821 (1 RCT)	⨁⨁◯◯ LOW [a,b]
Disease severity of participants who develop COVID-19 assessed with: Visual analogue scale (scores from 0 [no symptoms] to 10 [severe symptoms]) follow up: range 5 days to 14 days	"Among participants who were symptomatic at day 14, the median symptom severity score (on a scale from 0 to 10, with higher scores indicating greater severity) was 2.8 (interquartile range, 1.6 to 5.0) in those receiving hydroxychloroquine and 2.7 (interquartile range, 1.4 to 4.8) in those receiving placebo (P=0.34) "				821 (1 RCT)	-
Adverse reactions follow up: n/a	This outcome was not reported.				(1 RCT)	-
Adverse events assessed with: directed questioning for common side effects along with open-ended free text follow up: 14 days	145 per 1,000	**338 per 1,000** (258 to 444)	**RR 2.33** (1.78 to 3.06)		821 (1 RCT)	⨁⨁⨁◯ MODERATE [a]

Explanations

a. Downgraded by one level for serious indirectness - the events include those with laboratory and clinically confirmed cases, where the outcome of interest for this committee is laboratory confirmed cases.

b. Downgraded by one level for serious imprecision, low numbers of events, small sample size resulting in a wide confidence interval.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒ Uncertain ☐	1 trial, 821 participants. New COVID-19 infections (lab and clinically confirmed): RR 0.83 (95% CI 0.58 to 1.18). There would be 118 per 1,000 cases in the HCQ group compared to 143 per 1,000 (95% CI 83 to 168), that is 25 more cases per 1000 people exposed to COVID-19.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐ Uncertain ☐	No serious adverse events. 2-fold greater number of participants in the HCQ group reported adverse events.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐	
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	*High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☐ **Note:** As there was no evidence of benefit, the Committee did not adjudicate on feasibility.	Chloroquine is available as SAHPRA registered Nivaquine® and Plasmoquine®, but there have been historic supply challenges. Hydroxychloroquine 200 mg is equivalent to 155 mg chloroquine base; and 200 mg chloroquine sulfate is equivalent to 150 mg chloroquine base (British National Formulary, 2019 edition). **Note:** MHRA has stopped all prevention and treatment studies in the UK; and SAHPRA has suspended the prevention study in South Africa.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☐ **Note:** As there was no evidence of benefit, the Subcommittee did not adjudicate on resource use.	**Price of medicine/ treatment course** **Medicine** *(see note below)* / **Tender price*** / **SEP**** Chloroquine 200 mg x 19 tablets / n/a / R52.82 to R92.72 *Chloroquine is not currently on public sector contract. SEP price ranges from R2.78 to R4.88 per capsule/tablet, containing 200 mg chloroquine sulfate (Plasmoquine® and Nivaquine®, respectively). https://mpr.code4sa.org/ [Accessed 17 June 2020] ** SEP price (ex-dispensing fee) [Accessed 10 June 2020] https://mpr.code4sa.org/ **Note:** Treatment regimen is hydroxychloroquine 800mg immediately, 600mg 6-8 hours later, then 600mg daily for 4 days. - comparable estimated doses: HCQ 200 mg = chloroquine sulfate 200mg **Additional resources:** Safety monitoring and management of adverse drug reactions.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☐ **Is the option acceptable to key stakeholders?** Yes ☐ No ☐ Uncertain ☐ **Note:** As there was no evidence of benefit, the Committee did not adjudicate on values, preferences and acceptability.	People without COVID-19 would likely value additional methods to prevent transmission and prevention of illness and hospitalization with low safety concerns. No data about acceptability, but this medicine may be acceptable to stakeholders if use was supported by evidence that the benefit outweighed the harm.
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☐ Uncertain ☐ **Note:** As there was no evidence of benefit, the Committee did not adjudicate on equity.	This would depend on access and capacity to deliver the intervention to all who need it. We have not data on this.

Appendix 2: Search strategy

Database Epistemonikos (using the COVID-19 specific interface: https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d)

Search strategy: using their curated interface for any COVID-19 studies, any pharmacologic interventions (treatment or prevention). The main search term: chloroquine

Output: 501 records, 409 duplicates

Date: 10 June 2020

Database Cochrane COVID-19 study register (https://covid-19.cochrane.org/)

Search strategy: chloroquine

Output: 96 records, 12 duplicates

Date: 10 June 2020

Database Living mapping and living systematic review of Covid-19 studies (www.covid-nma.com)

Reviewed ongoing trials, https://covid-nma.com/networks/ (reported figure above)

One eligible study identified (summarized in this report)

Date: 10 June 2020

Appendix 3. Planned and ongoing studies (source: www.covid-nma.com 9 June 2020)

TREATMENT (PER ARM)	SAMPLE SIZE	SEVERITY AT ENROLLMENT	FUNDING	REG. NUMBER
(1) Hydroxychloroquine vs (2) Placebo vs (3) Lopinavir + ritonavir vs (4) Placebo	1200	Non ill health workers	Centre Hospitalier Universitaire de Saint Etienne	NCT04328285
(1) Hydroxychloroquine vs (2) Placebo	1600	Close contacts to covid patients	Columbia University	NCT04318444
(1) Hydroxychloroquine vs (2) Placebo	400	Non ill health workers	National Institute of Respiratory Diseases, Mexico	NCT04318015
(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo	3500	Non ill health workers	University of Minnesota	NCT04328467
(1) Hydroxychloroquine vs (2) Placebo	3000	Close contacts to covid patients	University of Minnesota	NCT04308668
(1) Hydroxychloroquine *vs* (2) Placebo	2000	Close contacts to covid patients	University of Washington	NCT04328961
(1) Hydroxychloroquine *vs* (2) Standard of care	2486	Close contacts to covid patients	Gangnam Severance Hospital	NCT04330144
(1) Hydroxychloroquine *vs* (2) Placebo	800	High risk patients	Instituto de InvestigaciÃ³n MarquÃ©s de Valdecilla	NCT04330495
(1) Hydroxychloroquine *vs* (2) Placebo	440	Non ill health workers	Barcelona Institute for Global Health	NCT04331834
(1) Hydroxychloroquine vs (2) Standard of care	3000	Close contacts to covid patients	Tan Tock Seng Hospital	NCT04342156
(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine vs (4) Placebo	1450	Healthy volunteers	United States Department of Defense	NCT04343677
(1) Hydroxychloroquine *vs* (2) Hydroxychloroquine *vs* (3) Standard of care	1530	Non ill health workers	Sociedad EspaÃ±ola de Farmacia Hospitalaria	EUCTR2020-001421-31-ES
(1) Hydroxychloroquine *vs* (2) Placebo	440	Non ill health workers	ISGlobal	EUCTR2020-001565-37-ES
(1) Lopinavir + ritonavir vs (2) Placebo vs (3) Hydroxychloroquine vs (4) Placebo	1200	Non ill health workers	CHU de Saint Etienne	EUCTR2020-001188-96-FR
(1) Hydroxychloroquine vs (2) Placebo	440	Non ill health workers	Medical University of Vienna	NCT04336748
(1) Hydroxychloroquine + bromhexine vs (2) Bromhexine	100	Non ill health workers	Instituto Nacional de Rehabilitacion	NCT04340349
(1) Hydroxychloroquine vs (2) Placebo	15000	Close contacts to covid patients	Duke University	NCT04334148
(1) Hydroxychloroquine vs (2) Hydroxychloroquine vs (3) Placebo	3000	Close contacts to covid patients	Henry Ford Health System	NCT04341441
(1) Emtricitabine vs (2) Hydroxychloroquine vs (3) Hydroxychloroquine + emtricitabine vs (4) Placebo	4000	Non ill health workers	Plan Nacional sobre el Sida (PNS)	NCT04334928
(1) Hydroxychloroquine vs (2) Placebo	500	Close contacts to covid patients	Tabriz University of Medical Sciences	IRCT20130306012728N8
(1) Hydroxychloroquine vs (2) Placebo	60	High risk patients	Mashhad University of Medical Sciences	IRCT20200405046958N1
(1) Hydroxychloroquine *vs* (2) Standard of care	1000	Close contacts to covid patients	Iran University of Medical Sciences	IRCT20190122042450N4