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

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

Date: 5 March 2021 *(update of the initial review dated 9 April 2020)*

Key findings

- We conducted a rapid review of available published clinical evidence regarding use of chloroquine or hydroxychloroquine with or without other medicines for patients with COVID-19.
- We found one systematic review, which included 12 randomised controlled trials of chloroquine or hydroxychloroquine compared to placebo, standard of care, or other active treatment.
- Chloroquine/hydroxychloroquine did not improve all-cause mortality (relative risk (RR) 1.09, 95% confidence interval (CI) 0.99 to 1.19, high certainty evidence) or progression to mechanical ventilation (RR 1.11, 95% CI 0.91 to 1.37, moderate certainty evidence).
- Chloroquine/hydroxychloroquine increased the risk of adverse events (RR 2.90, 95% CI 1.49 to 5.64, moderate certainty evidence), but not serious adverse events (RR 0.82, 95% CI 0.37 to 1.79, low certainty evidence).

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of 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)**
	X				

Recommendation: Chloroquine or hydroxychloroquine should not be used to treat patients with COVID-19.
Rationale: There is no evidence of benefit (moderate to high certainty evidence) but increased risk of harm (moderate certainty evidence).
Level of Evidence: I moderate to high certainty evidence

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)*.

BACKGROUND

Chloroquine and its derivative hydroxychloroquine were used for the treatment of malaria, before the development of widespread resistance, and are generally well tolerated. Hydroxychloroquine is more soluble and better tolerated than chloroquine but is not readily available in South Africa at present. Chloroquine is used to modulate immunity in rheumatoid arthritis and systemic lupus erythematosus patients.

There is *in vitro* evidence that chloroquine inhibits replication of SARS-CoV-2. Mechanisms include increasing pH in the intracellular endosome required for fusion of the virus with the cell, and inhibition of the entry of SARS-CoV-2 into cells through an effect on the ACE2 receptor (Liu 2020). In addition to suppression of viral replication, it was hypothesised that chloroquine's immunomodulatory effects may be of benefit in the treatment of COVID-19, (Wang 2020). Based on this theoretical benefit, during the current COVID-19 pandemic, chloroquine and hydroxychloroquine were included in treatment guidelines for COVID-19 in some countries.

Chloroquine and hydroxychloroquine may cause serious adverse reactions, including QT interval prolongation. This may put patients at risk of drug-induced torsades de pointes and sudden cardiac death. This risk is higher in elderly patients, those with congenital long QT syndrome and those taking other drugs which prolong the QT interval, such as azithromycin and lopinavir/ritonavir (Giudicessi 2020).

We reviewed current published evidence for efficacy and harms of chloroquine and hydroxychloroquine in treating patients with COVID-19.

METHODS

A Cochrane systematic review and meta-analysis was published on 12 Feb 2021. This rapid review includes the results and assessment of the Cochrane systematic review (Singh 2020). Results of the COVID-NMA living review (accessed 04 Mar 2021) were not substantially different to the published Cochrane review. No further searches were done for this rapid review.

RD summarised the included systematic review. TL and MR assessed the included systematic review using the AMSTAR tool. MB and KC reviewed the overall report.

Eligibility criteria for review

Population: Patients with COVID-19, no restriction to age or disease severity.

Intervention: Chloroquine or hydroxychloroquine either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator)

Outcomes: Mortality, hospitalisation, duration of hospitalisation, time to negative SARS-CoV2 PCR on nasopharyngeal swab, duration of ICU stay, progression to mechanical ventilation, adverse events, serious adverse events.

Study designs: For this review update we sought only systematic reviews of randomised controlled trials (RCTs).

RESULTS

The Cochrane review included 12 RCTs (8 569 participants in total) that compared chloroquine or hydroxychloroquine to placebo or standard of care (10 RCTs) or lopinavir/ritonavir (1 RCT), or febuxostat (1 RCT). One included RCT compared hydroxychloroquine plus azithromycin to standard of care. The results of relevance to our PICO as summarised below.

We assessed the methodological quality of the Cochrane review using the AMSTAR 2 tool (Appendix 1), which rated the overall confidence in the results of the review as 'moderate'.

The COVID-NMA meta-analysis includes a further 5 RCTs, but the results are not substantially different to the Cochrane review.

Hydroxychloroquine/ chloroquine compared with placebo/standard of care

- *All-cause mortality*

Chloroquine/hydroxychloroquine had no significant impact on mortality relative to placebo or standard of care: relative risk (RR) 1.09 (95% confidence interval (CI) 0.99 to 1.19), based on 9 RCTs, n=8 208, high certainty evidence.

- *Progression to mechanical ventilation*

Chloroquine/hydroxychloroquine had no significant impact on progression to requiring mechanical ventilation relative to placebo/standard of care: RR 1.11 (95% CI 0.91 to 1.37), based on 3 RCTs, n=4 521, moderate certainty evidence.

- *Duration of hospitalisation*

There was no significant difference in duration of hospitalization between hydroxychloroquine and standard of care/placebo: mean difference -0.15 days (95% CI -0.75 to 0.45), based on 2 RCTs, n=642.

- *Hospitalisation*

One RCT in ambulatory patients reported admission to hospital as an outcome: RR 0.41 (95% CI 0.13 to 1.27), n=465.

- *Time to negative PCR*

There was no significant difference in the proportion of patients who had negative PCR at 14 days between hydroxychloroquine/chloroquine and placebo/standard of care: RR 1.00 (95% CI 0.91 to 1.10), based on 3 RCTS, n=213, low certainty evidence.

- *Adverse events and serious adverse events*

Chloroquine/hydroxychloroquine increased the risk of adverse events relative to placebo/standard of care: RR 2.90 (95% CI 1.49 to 5.64), based on 6 RCTs, n=1 394, moderate certainty evidence.
Chloroquine/hydroxychloroquine was not associated with an increased risk of serious adverse events: RR 0.82 (95% CI 0.37 to 1.79), based on 6 RCTs, n=1 004, moderate certainty evidence.

Hydroxychloroquine/chloroquine compared with active treatments

One RCT compared hydroxychloroquine to lopinavir/ritonavir (n=22). Mortality, progression to mechanical ventilation, and duration of hospitalisation were no reported. There was no significant difference in time to negative PCR or risk of adverse events.

One RCT compared hydroxychloroquine to febuxostat (n=60). Progression to mechanical ventilation, duration of hospitalisation, and adverse events were no reported. There were no deaths in either arm. There was no significant difference in hospitalisation.

Hydroxychloroquine plus azithromycin compared with standard of care

One RCT compared hydroxychloroquine plus azithromycin to standard of care (n=444). There was no significant difference in mortality (RR 0.52, 95% CI 0.13 to 2.07), progression to mechanical ventilation (RR 1.61, 95% CI 0.82 to 3.15), duration of hospitalisation (mean difference 0.50 days, 95% CI -0.81 to 1.81), or serious adverse events (RR 1.85, 95% CI 0.36 to 9.43). Hydroxychloroquine plus azithromycin was associated an increased risk of adverse events: RR 1.74 (95% CI 1.27 to 2.38).

CONCLUSION

Hydroxychloroquine has been shown to have no significant impact on mortality or disease progression to mechanical ventilation but is associated with an increased risk of adverse events. Chloroquine or hydroxychloroquine should not be used to treat patients with COVID-19.

Reviewers: Karen Cohen, Marc Blockman, Renee de Waal.

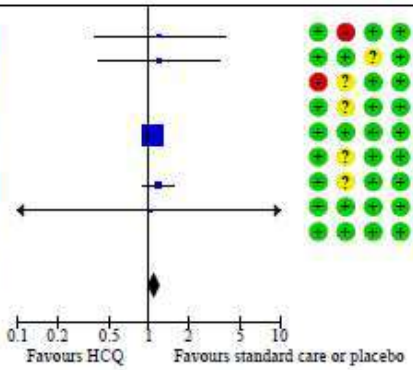
Declaration of interests: KC and MB (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) and RDW (Centre for Infectious Disease Epidemiology and Research, University of Cape Town) have no interests to declare in respect of chloroquine or hydroxychloroquine.

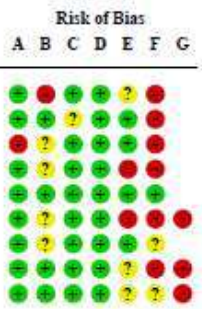
Acknowledgements: Trudy Leong (Essential Drugs Programme, National Department of Health) and Milli Reddy (Better Health Programme – South Africa) for assisting with the AMSTAR assessment.

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



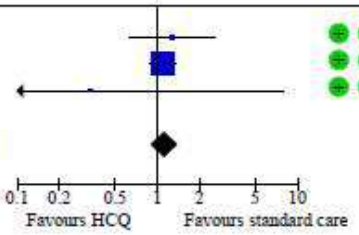


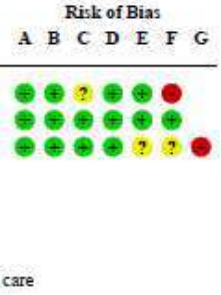
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.6. 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



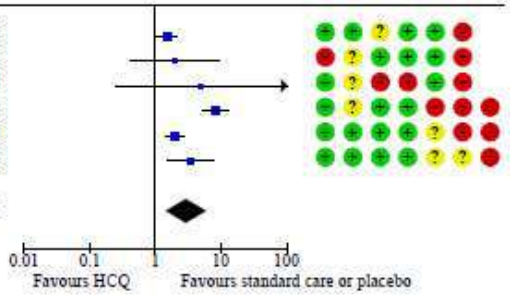


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting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

Analysis 1.10. 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.

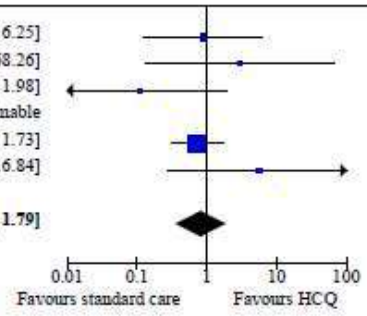
Risk of bias legend

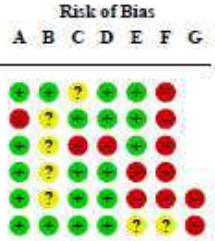
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other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

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

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(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Appendix 1: Evaluating the methodological quality of the Singh et al (2021) systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[1])

Date: 18 February 2021
Assessors: Trudy Leong, Milli Reddy

No.	Criteria	Yes/ Partial Yes/ No
1	Research questions and inclusion criteria for the review included the components of PICO	Yes
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes
3	Review authors explained selection of the study designs for inclusion in the review	Yes
4*	Review authors used a comprehensive literature search strategy	Partial yes
5	Review authors perform study selection and data extraction in duplicate	Yes
6	Review authors provided a list of excluded studies and justify the exclusions	Yes
7*	Review authors described the included studies in adequate detail	Yes
8	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes
9*	Review authors reported on the sources of funding for the studies included in the review?	Yes
10	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes
11*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes
12	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes
13*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes
14	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No
15*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes

** Critical domains*

Rating overall confidence in the results of the review
• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
• *Moderate:* More than one non-critical weakness**: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
(**Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Moderate

Rationale: Two non-critical flaws (#4:partial yes; and #14)

Conclusion: The AMSTAR assessment shows that the review has more than one non-critical weakness, but no critical flaws, and may provide an accurate summary of the results of the available studies that were included in the review

[1] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 2: 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 ☐	There are no benefits in terms of any clinically important outcomes.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	Hydroxychloroquine/chloroquine is associated with an increased risk of adverse events.
BENEFITS & HARMS	**Do desirable effects outweigh 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 ☐	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☐	N/A*
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☐	**Price of medicines:** N/A*
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 ☐	N/A*
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☐ Uncertain ☐	N/A*

* Judgements for these domains are not applicable, given the strong recommendation not to support use of hydroxychloroquine for treatment of COVID-19 due to the lack of evidence (benefit or harm).

Appendix 3: Updating of a rapid report

Date	Signal	Rationale
8 June 2020	Numerous RCTs published	Numerous RCTs published, but Cochrane review in progress

Version	Date	Reviewer(s)	Recommendation and Rationale
First	9 April 2020	TK, KC, MB, RdW	Insufficient evidence to recommend routine use of chloroquine or hydroxychloroquine for COVID-19; except in the context of a clinical trial.
Second	5 March 2021	RdW, KC, MB,	Chloroquine or hydroxychloroquine should not be used to treat patients with COVID-19 as there is no evidence of benefit but increased risk of harm.

References

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3. Giudicessi, J.R., Noseworthy, P.A., Friedman, P.A., and Ackerman, M.J. Urgent Guidance for Navigating and Circumventing the QTc Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for COVID-19. Mayo Clinic Proceedings. 2020; 95 https://mayoclinicproceedings.org/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_covid19.pdf
4. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst Rev. 2021 Feb 12;2:CD013587. https://pubmed.ncbi.nlm.nih.gov/33624299/