FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum

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Date: **May 21, 2020**

Subject: **Literature review on hydroxychloroquine or chloroquine use in COVID-19 population**

BACKGROUND

On March 28, 2020, FDA authorized the emergency use of hydroxychloroquine sulfate and chloroquine phosphate supplied from the Strategic National Stockpile. The criteria for treatment include adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible. On May 6, 2020, the Division of Antivirals (DAV) in the Office of Infectious Diseases (OID) consulted relevant divisions to review the published or available clinical trials, observational studies, and surveillance data and to comment on implications of these data regarding known or potential benefits and risks of the authorized use.

The Division of Epidemiology II (DEPI II), conducted a search of observational studies up to May 12, 2020 to identify high-quality evidence on the effectiveness or safety of hydroxychloroquine or chloroquine use in the COVID-19 population.

This memorandum summarizes DEPI II's assessment of the evidence from the observational literature.

REVIEW METHODS AND MATERIALS

The Stephen B. Thacker CDC Library has been collecting COVID-19 research articles, published since December 2019, in their "COVID-19 Research Articles Downloadable Database". This database is updated Mondays through Fridays and includes COVID-19 related literature from a systematic search of various bibliographic databases and a hand search of selected grey literature sources, such as archives of preprints research articles.[a]

We identified articles that contain "hydroxychloroquine" or "chloroquine" in the titles or abstracts from that database, provided on May 12, 2020.[b] We also considered manuscript proofs or preliminary findings of observational studies on hydroxychloroquine or chloroquine that were shared with FDA by the investigators.

[a] Complete list of databases searched: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, and LitCovid. Selected grey literature sources were searched as well, including the WHO COVID-19 website, CDC COVID-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

[b] Detailed search strings with synonyms used for COVID-19 can be found at the "Methodology" section of the CDC COVID-19 Research Articles Downloadable Database website
https://www.cdc.gov/library/researchguides/2019novelcoronavirus/researcharticles.html

Studies were considered for review if they were designed to evaluate the comparative effectiveness or safety of hydroxychloroquine or chloroquine use, and at a minimum have the following three design features:

1) Conducted in a population with confirmed COVID-19 infection
2) Reported quantitative estimates of treatment effectiveness or safety associated with hydroxychloroquine or chloroquine use,
3) A reference group that was not treated with hydroxychloroquine or chloroquine

REVIEW RESULTS

Search results

As of May 12, 2020, CDC's COVID-19 Research Articles Downloadable Database, included 27,519 articles. We identified 317 articles that mentioned "hydroxychloroquine" or "chloroquine" in their abstracts. Ten observational studies were eligible for review[1-10] after excluding non-observational studies (e.g. review, case report, case series, or randomized control trial), and studies that were not designed to evaluate hydroxychloroquine or chloroquine treatment outcomes in the COVID-19 population. We also included one study that was shared with FDA in manuscript proof format.[11] We summarized the study design, data source and methods of these 11 studies in Table 1.[c] *Of note, we also identified two comparative observational studies that assessed risk of cardiac adverse events, such as QT prolongation, Torsade de pointes or arrhythmogenic death with hydroxychloroquine or chloroquine use compared to hydroxychloroquine or chloroquine plus azithromycin (Mercuro 2020, Saleh 2020). These are events that can occur with hydroxychloroquine or chloroquine as well as azithromycin. However, since the studies did not include a non-hydroxychloroquine or chloroquine reference group, the results (had the studies been of good quality) could have only informed whether there was an increased cardiac risk with concurrent use of azithromycin and hydroxychloroquine or chloroquine compared to hydroxychloroquine or chloroquine alone. Therefore, we only described these studies in* ***Appendix A***

Briefly, all reviewed studies were cohort studies conducted in hospitalized COVID-19 populations, based on primary data collected prospectively by the investigators or secondary data retrospectively extracted from electronic medical records. Four of these studies were conducted in US, three in France, two in China, one in Saudi Arabia and one in Abu Dhabi. All studies reported findings on hydroxychloroquine or chloroquine treatment effectiveness, but only one study evaluated cardiac safety associated with hydroxychloroquine treatment.[8]

Of the 11 studies identified, only one study (Rosenberg et al) used sensitivity analyses to address limitations, which improved its quality compared to the other 10 studies. We consulted the Division of Biometrics VII (DB7) to review its statistical methods. This was also the only study to evaluate cardiac safety. Therefore, we provide a more detailed assessment of this study in this memorandum.

Main findings of the studies on effectiveness

Four studies used viral clearance as the primary effectiveness outcome[2,4,7,9] and seven used clinical events, such as all-cause mortality (e.g. Rosenberg et al.), intubation, ventilator use, transfer to intensive care, or various combinations of these clinical events.[1,3,5,6,8,10,11] As summarized in Table 2, the findings on the effectiveness

[c] The Division of Epidemiology II (DEPI II) became aware of a new publication by Mehra et al. on hydroxychloroquine or chloroquine use in the COVID-19 population on May 22, 2020, after the data lock date for our literature search. We provided overview of the new publication and our assessment in an addendum. The evidence provided in this new publication does not change our assessment of current evidence on hydroxychloroquine or chloroquine effectiveness or safety in COVID-19 population.

endpoints were inconsistent across all reviewed studies. Most of the point estimates reported were imprecise with confidence intervals that crossed the null.

Assessment of the major limitations of the studies reviewed studies

We identified major limitations of the 11 reviewed studies. These limitations also generally apply to the Rosenberg study discussed in more detail below:

1) Residual confounding, particularly confounding by disease severity

We observed that the hydroxychloroquine or chloroquine treated and untreated patient populations were heterogenous across the studies reviewed. In some studies, the hydroxychloroquine or chloroquine treated patients were older, had more comorbidities, or more severe COVID-symptoms at admission than the untreated patients,[3,5,8,10] while in other studies the treated patients were generally younger and "healthier" than the untreated group.[6,11] The bias introduced by patient selection can either under- or over-estimate effectiveness depending on patient characteristics.

The concern on residual confounding is most relevant to the four studies that examined viral clearance[2,4,7,9] and the Davido study that examined clinical outcomes,[1] because these studies either did not adjust for baseline characteristics,[2,4] adjusted for only few a covariates, or did not account for important characteristics that might affect disease prognosis, such as age, gender, and comorbidities.[1,7] Although the other studies attempted to adjust for more potential confounders and some employed advanced methods such as propensity scores, we are still uncertain that confounding was adequately addressed. For example, in the Geleris study the overlapping areas of the propensity score distribution by treatment groups were small,[2] which indicates that the comparison groups were very different at baseline. Also, because COVID-19 disease itself might be associated with cardiovascular adverse events, confounding by disease severity could still bias the study that examined cardiac safety outcome in that study.

2) Selection of index time, potential for immortal time bias, and insufficient confounding adjustment

Nine of the 11 reviewed studies set the index time (baseline) for analysis at the time of hospital admission for COVID-19 infection, instead of the time of hydroxychloroquine or chloroquine initiation for the treated group. For the studies that included mortality as endpoint,[1,3,5,6,8,10,11] this would introduce "immortal time" in the treated group, which would lead to an under-estimation of mortality risk, as only those who survived to treatment initiation could be included in the hydroxychloroquine treatment group. For the study that examined cardiac safety outcomes (Rosenberg et al),[8] starting the index time prior to treatment initiation would lead to over-estimation of cardiac risk associated with treatment, because the observed outcome event could have occurred before treatment initiation, but would be erroneously counted as an event in the hydroxychloroquine treatment group.

It should be noted, the "immortal time" in the analyses was not the only methodological issue caused by the selection of index time. The index time issue would also lead to insufficient control of the differences in COVID-19 disease severity or underlying cardiac risk between the treated and untreated group, because the captured "baseline" COVID-19 symptoms or cardiac conditions might not be predictive of the COVID-19 disease severity at treatment initiation. Therefore, we cannot conclude that any individual study clearly under-estimated or over-estimated the relative risk.

3) Other methodologic issues

In most of the reviewed studies, the patients in the "reference group" usually received other medications or supportive treatment for COVID-19 (such as antiviral treatment or antibiotics); however, it was not clearly defined or described in their reports. It also was not always clear if the treated group also received other

COVID-19 medications or whether the extent of supportive care measures was similar to that in the reference group. A poorly defined reference group makes it difficult to interpret the effectiveness, or safety findings.

Most of the reviewed studies did not report a prior power calculation. Given that most effect estimates reported had wide confidence intervals, the reviewed studies were likely underpowered to detect effectiveness or safety outcomes. In addition, generalizability of the findings of these studies was limited because they were conducted in either a single institution or a single region or country, and in mostly small patient populations.[d]

The Rosenberg study

The Rosenberg study is a retrospective multicenter cohort study that included a sample of patients with laboratory-confirmed COVID-19 randomly selected from all admitted patients within 25 hospitals (the 25 hospitals accounted for 88% of hospitalized patients with laboratory-confirmed COVID-19 in the New York metropolitan region). Eligible patients were admitted for at least 24 hours between March 15 and 28, 2020. The primary effectiveness outcome was in-hospital mortality. After adjustment for demographic characteristics, hospital, preexisting conditions and illness severity, no significant differences in mortality were found between patients receiving hydroxychloroquine + azithromycin, hydroxychloroquine alone or azithromycin alone compared with neither drug (Table 2).

The secondary cardiac safety outcomes were cardiac arrest and abnormal ECG findings (e.g. arrhythmia or QT prolongation), ascertained from medical records.[8] Compared to patients who received neither hydroxychloroquine nor azithromycin, risks of cardiac arrest and abnormal ECG findings were higher among patients receiving hydroxychloroquine + azithromycin, and those receiving hydroxychloroquine alone, although the risk estimates were not statistically significant for the monotherapy group (Table 2).

However, these findings on the effectiveness or safety of hydroxychloroquine treatment in the COVID-19 population still needs to be interpreted with caution due to the limitations described above, even though the investigator attempted to address some of those limitations. We elaborate on our concerns below.

The study included a sensitivity analysis that used time-dependent treatment status, which accounted for immortal time.[8] This sensitivity analysis still could not sufficiently adjust for the differences in COVID-19 disease severity between the treated and untreated group, due to the fact that the analysis did not adjust for certain important indicators of COVID-19 severity, such as mechanical ventilation initiation,[e] and that the adjusted "baseline" characteristics were not captured at treatment initiation for the treated groups. The residual confounding could lead to either under- or over-estimation of the mortality risk.

As for the findings on safety endpoints, the Rosenberg study was the only study that conducted comparative analyses on cardiac safety endpoints between hydroxychloroquine treated and non-treated patients. Although the information on cardiac safety endpoints were ascertained from chart review, the author did not provide clear outcome definitions on cardiac arrest, how they identified these outcomes from the charts, nor provided data to support the validity of the outcome events identified from medical records. The observed cardiac risk associated with hydroxychloroquine could be biased because death due to cardiac arrest was not included as a safety outcome, and that "abnormal ECG" findings would only occur among patients who had ECG during the follow-up period. This outcome misclassification would lead to underestimation of absolute risk and under- or over-estimation of relative risk. Although it was not statistically significant, the study observed that azithromycin is associated with a lower risk of cardiac arrest or abnormal ECG findings, versus no treatment. Given that azithromycin is known to be associated with QT prolongation and have been reported to increase

[d] Six of the reviewed studies had <100 hydroxychloroquine or chloroquine treated patients, one had between 100-200 treated patients, and four had >200 treated patients. The largest study (Rosenberg et al.) included 1,006 treated patients.

[e] Rosenburg et al. attempted to account for mechanical ventilation initiation status using stratified analyses, however, the "mechanical ventilation status" was ascertained incorrectly for the stratified analyses. Specifically, it included those that were initiated during the follow-up period. These events happened during follow-up period should not had been used to categorized patient's mechanical status given that the treatment can impact mechanical ventilation initiation.

cardiovascular mortality,[12] this observation could indicate residual confounding in the analyses of safety outcomes in this study.

Although the investigators performed a power analysis, the assumptions for that analysis appear to be different from the observed treatment effect size and background mortality rate. The sample size estimation should be based on the "number of events needed", instead of "the sample size needed", as the primary analysis used Cox proportional model. Therefore, the study power was likely lower than the prespecified power for effectiveness endpoints.

Lastly, the treatment regimen for the treated group and the medical care provided to the untreated population were not clearly described, and we do not know if they were consistent across the 25 hospitals included in the study as the standards of care were not reported. This made it hard to interpret the study findings.

Although it is the largest study to date that examined hydroxychloroquine use in COVID-19 population, the generalizability is still limited given that it was restricted to a single metropolitan area. The findings also only apply to COVID-19 patients who were admitted to hospital for more than 24 hours, because the study excluded patients who were discharged or died within the first 24 hours of hospitalization.

CONCLUSION

As of May 12, 2020, 11 observational studies were identified that quantified the comparative effectiveness or cardiac safety of hydroxychloroquine or chloroquine treatment in hospitalized COVID-19 patients. The observed treatment effectiveness was inconsistent across these studies and could either over- or under-estimate the true benefit due to study limitations. Most importantly, there were limitations such as residual confounding, especially the insufficient control of COVID-19 disease severity, and immortal time bias.

The trend of elevated risk of adverse cardiac outcomes associated with hydroxychloroquine with or without azithromycin observed in the one study (Rosenberg et al) that examined cardiac safety is in general aligned with the biological plausibility; however, there is still concern over residual confounding and bias due to outcome misclassification, that could lead to underestimation of absolute risk and under-or over-estimation of the relative risk.

Currently, the available observational data are of insufficient quality to inform the effectiveness or safety of hydroxchloroquine or chloroquine use in the COVID-19 population.

Table 1. Summary of observational effectiveness or safety studies of hydroxychloroquine or chloroquine use in COVID-19 patients

Effectiveness studies

Author	Study design; Country; Study period; Data source	Population	Treatment	Reference	Main Outcome	Index time	Adjusted covariates
Rosenberg E	Retrospective cohort study; US; 3/15-4/24/2020; primary data collection (chart abstraction) from 25 hospital in a single metropolitan region	Random sample of patients hospitalized with confirmed COVID-19 admitted for 24+ hours between 3/15-28/2020	**HCQ*** **HCQ+AZM*** **AZM***	**Non-HCQ, nor AZM***	Mortality	24 hours after admission	Age, sex, hospital, diabetes, chronic lung disease, CVD (hypertension, coronary artery disease, congestive heart failure), respiratory rate >22/min, O2 saturation <90%, abnormal chest imaging findings, AST>40 U/L, and elevated creatinine levels
Geleris J	Retrospective cohort study; US; 3/7 to 4/25/2020	Hospitalized patients with confirmed COVID-19 test. Excluded patients who were intubated, died, or were transferred to another facility within 24 hours after presentation to the ER	**HCQ** 600mg twice Day 1 then 400mg daily for 4 additional days	**Non-HCQ**‡	Intubation or death	24 hours after presentation to the ER	PS calculated by age, sex, race, BMI, insurance, smoking, comorbidities, concurrent medications, vital and laboratory tests at presentation to ER
Huang M	Prospective cohort study; China; 2/7-3/8/2020; Primary data collected by investigators from 12 hospitals in 2 provinces	Hospitalized patients with confirmed COVID-19 who did not meet the exclusion criteria‡	**CQ** 500 mg PO, once/twice-daily up to 10 days	**Non-CQ** treated with other COVID-19 Meds	Time to undetectable viral RNA	Treatment initiation	Did not conduct adjusted analysis
Mallat J	Retrospective cohort study; Abu Dhabi; 3/1-3/25/2020; EMR of a single hospital	Hospitalized patients with confirmed COVID test	**HCQ** 400 mg twice daily Dy 1, followed by 400 mg daily for 10 days	**Non-HCQ**‡	Time to SARS-CoV-2 negativity test	Date of the first confirmed covid-19 test	Symptoms and development of pneumonia during hospitalization
Yu B	Retrospective cohort; China; 2/1-4/8/2020; EMR of a single hospital	Hospitalized, critically ill※, confirmed COVID-19 patients	**HCQ** 200 mg twice a day for 7-10 days+ Basic COVID-19 treatment	**Non-HCQ** treated with basic COVID-19 Meds	Mortality	Unclear	Age, sex, history of hypertension, diabetes mellitus, coronary heart disease, and COPD, and oxygen saturation, baseline treatment drug
Magagnoli J	Retrospective cohort study; US (3/9-411);	Hospitalized male patients with confirmed COVID test and	**HCQ, HCQ+AZM***	**Non-HCQ**‡	Mortality	Hospital admission	Demographic (age, sex, race, BMI), Charlson comorbidity score, heart

Effectiveness studies							
Author	**Study design; Country; Study period; Data source**	**Population**	**Treatment**	**Reference**	**Main Outcome**	**Index time**	**Adjusted covariates**
	VA informatics and computing infrastructure	complete info on BMI, vital signs during encounter and discharge disposition					rate, pulse oximetry, respirations, temperature, and blood pressure, ACE/ARB use
Ip A	Retrospective cohort study; US 3/1-4/8; EHR of a hospital network	Hospitalized patients with confirmed COVID-19 test who are not pregnant, not on RCT and did not die during first day of hospitalization	**HCQ, HCQ+AZM***	**Non-HCQ**‡	Mortality	Hospital admission	A risk score calculated by sex, age, whether patients entered directly to ICU, serum ferritin, insulin use, and arrhythmia
Mahevas M	Cohort study; France; 3/17-3/31/2020; EHR of 4 tertiary care centers	Hospitalized patients with confirmed COVID-19 test and required oxygen by mask or nasal prongs, and not met the exclusion criteria[¶]	**HCQ** at 600 mg/day, initiated in first 2 days of hospitalization	**Non-HCQ**‡: Absence of HCQ initiation during first 2 days of hospitalization	Transfer to ICU in 7 days and/or death	Hospital admission	PS calculated by: Age; gender; comorbidities; BMI (≥30 kg/m^2 or not); third trimester of pregnancy; treatment by ACEI/ARB, time since symptom onset; severity of condition admission
Gautret P	Open label non-randomized trial; France; Early march to March 16, 2020; Primary collected data	Hospitalized patients with confirmed COVID-19 test and not met the exclusion criteria[€]	**HCQ** 200mg 3 times/day for 10 days	**Non-HCQ**‡: Patients who refused HCQ or met the exclusion criteria in the same center or in the other center	Virological clearance at Day 6	Hospital admission	Did not conduct adjusted analysis
Shabrawishi	Retrospective cohort study; Saudi Arabia; 3/7-4/15/2020; single institution, did not describe data source	Hospitalized patients (12+ yrs) with confirmed test, excluding patients admitted or transferred to ICU or transferred to other facility	**HCQ/CQ; HCQ/CQ+AZM; HCQ/CQ, antivirals ± AZM**	**No treatment**‡ Supportive care	Negative conversion rate of SARS-COV-2 nasopharyngeal PCR by Day 5 of treatment initiation	Treatment initiation for treated group, hospital admission for untreated	Age, gender, and disease severity
Davido	Retrospective cohort study; France; 3/2-4/17/2020; primary collected data from a single institution	Hospitalized adult patients with confirmed test, excluded patients discharged from ICU to medicine ward, and those	**HCQ+AZM for 48 hours** HCQ: Loading dose of 800mg on Day 1 then 400-	**No treatment, other COVID-19 treatment or HCQ+AZM less than 48 hours**	"Favorable" outcome, and the definition was unclear	Hospital admission	Did not conduct adjusted analysis

Effectiveness studies							
Author	**Study design; Country; Study period; Data source**	**Population**	**Treatment**	**Reference**	**Main Outcome**	**Index time**	**Adjusted covariates**
		who did not agree to data collection	600mg/day for 10 days AZM: 500mg on Day 1, then 250mg for 4 days				
Safety study							
Author	**Study design; Country; Study period; Data source**	**Population**	**Treatment**	**Reference**	**Main Outcome**	**Index time**	**Adjusted covariates**
Rosenberg E	Retrospective cohort study; US; 3/15-4/24/2020; primary data collection (chart abstraction) from 25 hospitals in a single metropolitan region	Random sample of patients hospitalized with confirmed COVID-19 admitted for 24+ hours between 3/15-28,2020	**HCQ*** **HCQ+AZM*** **AZM ***	Non-HCQ, nor AZM*	Cardiac arrest and abnormal ECG findings (arrhythmia or QT prolongation)	24 hours after admission	Age, sex, hospital, diabetes, chronic lung disease, CVD (hypertension, coronary artery disease, congestive heart failure), respiratory rate >22/min, O_2 saturation <90%, abnormal chest imaging findings, AST>40 U/L, and elevated creatinine levels

HCQ: hydroxychloroquine, CQ: Chloroquine; AZM: azithromycin; TdP: torsades de pointes; EMR: electronic medical record; PS: propensity score; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers, CVD: cardiovascular disease, BMI: body mass index

[T] Huang et al. excluded patients if he/she met any of the following criteria: pregnant women, with known allergies to 4-aminoquinoline compounds, blood system diseases, chronic liver or kidney diseases in end-stage, arrhythmia or second/third degree heart block, with known to have retinopathy, hypoacusis or hearing loss, mental disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, had received digitalis drugs within the 7 days preceding enrollment, or is classified as critical case according to China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (4th Edition)

[※] Critically ill in Yu B et al. was defined as meeting one of the following: 1) had respiratory failure and needed mechanical ventilation; 2) had septic shock during hospitalization; 3) with other organ failures that required monitoring and treatment in ICU

[Þ] Mahevas study exclusion criteria: 1) the presence of a contraindication to HCQ at 600 mg daily (including patients under dialysis); 2) the start of HCQ before admission to the hospital; 3) treatment with another experimental drug for COVID-19 (tocilizumab, lopinavir-ritonavir, or remdesivir) within 48 hours after admission; 4) organ failure requiring immediate admission to the ICU or continuous care unit (CCU); 5) ARDS at admission (defined by the need for non-invasive ventilation with provision of positive airway pressure or invasive mechanical ventilation); 6) discharge from the ICU to standard care; 7) decision to limit and stop active therapeutics made at admission); and 8) opposition to data collection by the patient or her/his legal representative.

[€] Gautret study exclusion criteria: Patients were excluded if they had a known allergy to hydroxychloroquine or chloroquine had another known contraindication to treatment with the study drug, including retinopathy G6PD deficiency and QT prolongation. Breastfeeding and pregnant patients were excluded based on their declaration and pregnancy test results when required

*Did not include information on HCQ or CQ treatment regimen;

[‡] Did not include information on the COVID-19 given to the reference group

Table 2. Main findings of observational effectiveness or safety studies of hydroxychloroquine or chloroquine use in COVID-19 patients

Effectiveness studies-Clinical events

Author	Main Outcome	Treatment n outcome n (%)	Reference n/ outcome n (%)	Effect estimates	Adjusted covariates
Rosenberg	Mortality	HCQ=271 54 (20%) HCQ+AZM=735 189 (26%) AZM=211 21 (10%)	Non-HCQ nor AZM=211 28 (13%)	Crude HR unavailable aHR HCQ=1.08 (0.60-1.85) aHR HCQ+AZM=1.35 (0.76-2.40) aHR AZM=0.56 (0.26-1.21)	Age, sex, hospital, diabetes, chronic lung disease, CVD (hypertension, coronary artery disease, congestive heart failure), respiratory rate >22/min, O2 saturation <90%, abnormal chest imaging findings, AST>40 U/L, and elevated creatinine levels
Geleris J	Intubation or death	HCQ=811 262 (32.3%)	Non-HCQ=565 84 (14.9%)	Crude HR=2.37 (1.84-3.02) IPW HR=1.04 (0.82-1.32)	Age, sex, race, BMI, insurance, smoking, comorbidities, concurrent medications, vital and laboratory tests at presentation to ER
Yu B	Mortality	HCQ (n=48) 9 (18.8%)	Non-HCQ (n=520) 238 (45.8%)	Crude HR=0.33 (0.17-0.64) aHR=0.33 (0.17-0.65)	Age, sex, comorbidities (hypertension, diabetes mellitus, coronary heart disease, and COPD), and oxygen saturation, baseline treatment drug
Magagnoli J	Mortality	HCQ=97 27 (27.8%) HCQ+AZM=113 25 (22.1%)	Non-HCQ=158 18 (11.4%)	Crude HR unavailable aHR HCQ=2.61 (1.10-6.17) aHR HCQ+AZM=1.14 (0.56-2.32)	Age, sex, race, BMI, Charlson comorbidity score, heart rate, pulse oximetry, respirations, temperature, and blood pressure, ACE/ARB use
Ip A	Mortality	HCQ=202 HCQ+AZM=666 Outcome n unavailable	Non-HCQ=115 Outcome n unavailable	Crude HR unavailable aHR HCQ= 1.02 (0.59-1.74) aHR HCQ+AZM= 0.89 (0.42-1.87)	A risk score calculated by age, sex, whether patients entered directly to ICU, serum ferritin, insulin use, and arrhythmia
Mahevas M	Transfer to ICU in 7 days and/or death	HCQ=84 16 (19%)	Non-HCQ=97 21 (21.6%)	Crude RR=0.88 (0.49-1.57) IPTW RR=0.93 (0.48-1.81)	Age; sex; comorbidities; BMI; third trimester of pregnancy; treatment by ACEI/ARB, time since symptom onset; severity of condition admission
Davido	"Favorable outcome"	HCQ+AZM for 48 hours after admission (n=45)	No treatment or other COVID-19 treatment HCQ+AZM less than 48 hours (n=87)	Patients receiving HCQ+AZM ≥48hrs had a greater likelihood for a favorable outcome (OR=6.2) than the reference group	Did not conduct adjusted analysis

Effectiveness studies-Viral clearance

Author	Main Outcome	Treatment	Reference	Main findings	Adjusted covariates
Huang M	Time to undetectable viral RNA	CQ (n=197)	Non-CQ (n=176)	Median time to achieve an undetectable viral RNA was shorter in CQ than in non-CQ AD = -6 days (-6.0 to -4.0)	Did not conduct adjusted analysis

Effectiveness studies-Clinical events					
Author	**Main Outcome**	**Treatment n outcome n (%)**	**Reference n/ outcome n (%)**	**Effect estimates**	**Adjusted covariates**
Mallat J	Time to SARS-CoV-2 negativity test	HCQ (n=21)	Non-HCQ (n=13)	The time to SARS-CoV-2 negativity test was longer in HCQ group than non-HCQ (17 [13-21] vs. 10 [4-13] days). HCQ treatment was independently associated with a longer time to negativity test (β coefficient=5.68 (1.05-10.08)	Symptoms and development of pneumonia during hospitalization
Gautret P	Viral clearance at Day-6	HCQ (n=26)	Non-HCQ (n=16)	At Day 6, 70% of (more) HCQ patients were cured (viral clearance) compared with 12.5% in non-HCQ (p= 0.001).	Did not conduct adjusted analysis
Shabrawishi	Negative conversion rate of SARS-COV-2 nasopharyngeal PCR by day 5 of treatment initiation	HCQ/CQ (n=15) HCQ/CQ+AZM (n=25) HCQ/CQ, antivirals ± AZM (n=5)	No treatment (n=48)	No statistically significant difference between any intervention groups and reference group in achieving the primary endpoint in the adjusted analyses, but did not report the effect estimates	Age, gender, and disease severity
Safety study					
Author	**Main Outcome**	**Treatment**	**Reference**	**Main findings**	**Adjusted covariates**
Rosenberg E	Cardiac arrest	HCQ=271 37 (14%) HCQ+AZM=735 114 (16%) AZM=211 13 (6%)	Non-HCQ nor AZM=211 15 (7%)	aOR HCQ=1.91 (0.96-3.81) aORHCQ+AZM=2.13 (1.12-4.05) aOR AZM=0.64 (0.27-1.56)	Age, sex, hospital, diabetes, chronic lung disease, CVD (hypertension, coronary artery disease, congestive heart failure), respiratory rate >22/min, O2 saturation <90%, abnormal chest imaging findings, AST>40 U/L, and elevated creatinine levels
Rosenberg E	Abnormal ECG findings (arrhythmia or QT prolongation)	HCQ=271 73/233 (31%) HCQ+AZM=735 192/634 (30%) AZM=211 34/180 (19%)	Non-HCQ nor AZM=211 31/155(20%)	aOR HCQ=1.50 (0.88-2.58) aORHCQ+AZM=1.55 (0.89-2.67) aOR AZM=0.95 (0.47-1.94)	Age, sex, hospital, diabetes, chronic lung disease, CVD (hypertension, coronary artery disease, congestive heart failure), respiratory rate >22/min, O2 saturation <90%, abnormal chest imaging findings, AST>40 U/L, and elevated creatinine levels

HCQ: hydroxychloroquine, CQ: Chloroquine; AZM: azithromycin; aOR: adjusted odds ratio; aHR: adjusted hazard ratio, ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers, CVD: cardiovascular disease, ICU: intensive care unit, ER: emergency room

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Appendix A

In the literature search, we identified two comparative observational studies that assessed risk of cardiac adverse events, including QT prolongation, Torsade de pointes (TdP) caused by QT prolongation, or arrhythmogenic death, associated with QT prolongation with hydroxychloroquine/chloroquine use compared to hydroxychloroquine/chloroquine + azithromycin (another known cardiotoxic drug) (Mercuro 2020, Saleh 2020). Both studies observed the concurrent treatment of azithromycin is associated with a greater increased in QT interval.

The Saleh study did not observe any serious cardiac events (TdP or arrhythmogenic death) among the 201 patients who were treated with hydroxychloroquine or chloroquine ± azithromycin. Seven patients (3.5%) needed to discontinue the medications due to QT prolongation, and two additional patients were treated with intravenous lidocaine that shortened the QT allowing for continuation of hydroxychloroquine. In the Mercuro study, ten patients (11%) stopped taking hydroxychloroquine prior to Day 5 of treatment for QT prolongation; one patient who had hydroxychloroquine and azithromycin developed TdP 3 days after discontinued the treatment and subsequently developed other ventricular arrhythmias that were treated with lidocaine.

However, in the Mercuro study baseline differences between the two treatment groups were not adjusted for in their comparison of the treatment outcome (e.g. patients that received combination therapy tended to have more severe COVID-19 symptoms, more comorbid conditions, and were more likely to concurrently use loop diuretics). In the Saleh study, the baseline patient characteristics differences were not described by treatment groups.

Also, since the studies did not include a reference group of non-hydroxychloroquine/chloroquine treated patients, the results (had the studies been of good quality) could have only informed whether there was increased cardiac risk with concomitant use of azithromycin and hydroxychloroquine or chloroquine compared to hydroxychloroquine or chloroquine alone. Also, neither study could rule out that these cardiac events might due to COVID-19 associated stress cardiomyopathy or myocarditis.

Finally, the observed frequencies of the severe cardiac adverse events might not be generalizable to other hydroxychloroquine or chloroquine treated COVID-19 population, given that the study populations were under close monitoring for cardiac adverse events (about 80% of patients had a follow-up ECG during treatment and all patients received twice daily EKGs (Mercuro study) or mobile cardiac outpatient telemetry patch during treatment (Saleh study).

Addendum

The Division of Epidemiology II (DEPI II) became aware of a new publication by Mehra et al.[a] on hydroxychloroquine or chloroquine use in the COVID-19 population on May 22, 2020, after the data lock date for our literature search review summarized in the DEPI II memo.
We provide an overview of the new publication and our assessment in this addendum. The evidence provided in this new publication does not change our assessment of current evidence on hydroxychloroquine or chloroquine effectiveness or safety in the COVID-19 population.

Overview of study methods

Mehra et al conducted a retrospective study based on a multinational registry to compare the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents.[b] The study included patients with a positive laboratory finding for SARS-CoV-2 who were hospitalized between Dec 20, 2019, and April 14, 2020, and completed their hospital course (discharged or died) before April 21, 2020.[c] Patients who received one of the treatments of interest within 48 hours of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients not on one of these regimens formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or ventricular fibrillation) (Table 1).

Table 1. Summary of Mehra study design

Study design; Country; Study period; Data source	Population	Treatment	Reference	Main Outcome	Index time
Retrospective cohort study; global; 12/20/2019-04/21/2020; EMR from 671 hospitals in six continents	Hospitalized patients with confirmed COVID-19 test between Dec 20, 2019, and April 14, 2020, and completed their hospital course (discharged or died) before April 21, 2020. Excluded patients who initiated treatments > 48 h after diagnosis or while they were on mechanical ventilation, and,patients who received remdesivir	**HCQ* HCQ+macrolide* CQ* CQ+macrolide***	**No-HCQ, nor CQ**	Mortality and occurrence of de-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or ventricular fibrillation)	Hospital admission

HCQ: hydroxychloroquine, CQ: Chloroquine; EMR: electronic medical record; *Did not include information on HCQ or CQ treatment regimen;

[a]Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. Published online May 22, 2020 https://doi.org/10.1016/S0140-6736(20)31180-6

[b] Distribution of hospital: 559 (83%) in North America, 50 (7%) in Europe, 30 (4%) in Africa, 18(3%) in South America, 9(1%) in Asia, 5(0.7%) in Australia.

[c] Patients who were hospitalized during the study period without a completed course were unable to be analyzed.

Main findings

A total of 96,032 patients (mean age 53.8 years, 46% women) with COVID-19 were included in the study. Of these, 14,888 (16%) patients were in the treatment groups (1868 [2%] received chloroquine, 3783[4%] received chloroquine with a macrolide, 3016[3%] received hydroxychloroquine, and 6221[7%] received hydroxychloroquine with a macrolide) and 81,144 (84%) patients were in the control group. Eleven percent (n=10,698) of patients died in hospital. In the adjusted analyses, when compared with the control group, the four treated groups were each independently associated with an increased risk of in-hospital mortality and de-novo ventricular arrhythmia during hospitalization (Table 2).

Table 2. Main findings of Mehra study

Outcome	Treatment n outcome n (%)	Reference n/ outcome n (%)	Effect estimates	Adjusted covariates
Mortality	HCQ=3,016 543 (18%) HCQ+ macrolide=6,211 1,479 (23.8%) CQ=1,868 307 (16.4%) CQ+ macrolide=3,783 839 (22.2%)	No-HCQ, nor CQ*=81,144 7530 (9.3%)	Crude HR unavailable aHR HCQ=1.34 (1.22-1.46) aHR HCQ+macrolide=1.45 (1.37-1.53) aHR CQ=1.37 (1.22-1.53) aHR CQ+macrolide=1.37 (1.27-1.47)	Age, sex, race or ethnicity, comorbidities (BMI, presence of coronary artery disease, presence of congestive heart failure, history of cardiac arrhythmia, diabetes, or COPD, current smoker, history of hypertension, immunocompromised state, and history of hyperlipidaemia), medications (ACEI, ARB, statin, antivirals), and severity of illness scores (qSOFA <1 and SPO2 <94%)
De-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or ventricular fibrillation)	HCQ=3,016 184 (6.1%) HCQ+ macrolide=6,211 502 (8.1%) CQ=1,868 81 (4.3%) CQ+ macrolide=3,783 246 (6.5%)	No-HCQ, nor CQ*=81,144 226 (0.3%)	Crude HR unavailable aHR HCQ= 2.37 (1·94–2·90) aHR HCQ+macrolide= 5.11 (4.38–5.98) aHR CQ= 3.56 (2.76–4.60) aHR CQ+macrolide= 4.01 (3.34–4.81)	**Same as above**

HCQ: hydroxychloroquine, CQ: Chloroquine; EMR: electronic medical record; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers, BMI: body mass index; COPD: chronic obstructive pulmonary disease; SPO2: Oxygen saturation; qSOFA: quick sequential organ failure assessment

Assessment of the study

DEPI identified major limitations in this study. While the author provided a general overview of the source data; there was **insufficient information** to assess the quality of the data collected.

Missing data

It was mentioned that "*A manual data entry process is used for quality assurance and validation to ensure that key missing values are kept to a minimum.*" However, the author did not discuss the degree of missing values for the data elements used in the study analyses. Previous research that utilized data based on manual extraction of patient medical records (Rosenberg et al.) to examine hydroxychloroquine use in a hospitalized COVID-19 population reported that about a

quarter of patients had missing values on the information needed to ascertain important confounders, such as smoking status (25%) and obesity (body mass index, 28%).

Unmeasured and under-ascertainment of important confounders

The study did not report several comorbidities and laboratory results that have been associated with COVID-19 severity and mortality, such as chronic kidney disease, cancer, chronic lung disease (other than COPD), elevated liver enzymes. It also did not include other variables that had been used as a proxy for patients' underlying disease severity in previous studies, such as abnormal chest image findings or whether patients directly went to the ICU on admission for COVID-19.

Furthermore, some comorbidities seem to be under-reported or not reported in this study compared to other studies that also evaluated hydroxychloroquine or chloroquine use in COVID-19 populations. To illustrate the magnitude of potential under-ascertainment or absence of important confounders, we compared the observed frequency of selected baseline characteristics in the COVID-19 population in North America (65% of the overall population in this study [of note: >90% of cases in the North America are from the US]) to two publications that described COVID-19 patients admitted to multiple US hospitals during a similar timeframe (Table 3).

The author also did not provide the diagnosis codes used to ascertain the underlying comorbidities, so it is unclear how well these variables were captured. The impact of residual confounding due to unmeasured or incompletely measured confounders can lead to either under- or over-estimation of the observed outcome risks. The author conducted a "tipping point analysis" to address the impact of residual confounding, and interpreted the result under the assumption that there would only be a single unmeasured confounder.[d] However, the aggregate frequency or association of the multiple unmeasured or incompletely captured confounders in the study could reach the frequency or strength of association that is needed to tip the observed association to non-significance at the 5% level.

[d] For the observed HR on Chloroquine, hydroxychloroquine, and chloroquine with second-generation macrolide: *"a hypothetical unobserved binary confounder with a prevalence of 50% in the exposed population would need to have a hazard ratio of 1.5 to tip this analysis to non-significance at the 5% level."* For the observed HR for hydroxychloroquine and second-generation macrolide treatment: "a hypothetical unobserved binary confounder with a prevalence of 37% in the exposed population would need to have a hazard ratio of 2.0 to tip this analysis to non-significance at the 5% level."

Table 3 Selected patients characteristics in studies on hydroxychloroquine or chloroquine use in COVID-19

	Mehra (North America)	CDC COVID-NET[e]	Rosenberg et al.
Source population	COVID-19 patients admitted to 559 hospitals in North America 12/20/19-04/17/20	COVID-19 patients admitted to hospitals in 99 counties in 14 US States in 03/01-03/30/2020	COVID-19 patients admitted to 25 hospitals in metro-NYC 03/15-03/28/20
N	63,315	1,482	1,438
Age	Mean 54±18	-	Median 63
Female	29288 (46%)	677 (46%)	580 (40%)
Hypertension	17,157 (27%)	79/157 (50%)	816 (57%)
CHF	1639 (3%)	11/162 (7%)	96 (7%)
Diabetes	8654 (14%)	47/166 (28%)	504 (35%)
COPD	2069 (3%)	17/159 (11%)	-
Chronic lung disease	Not reported	55/159 (35%)	259 (18%)
Cancer	Not reported	-	55 (3.8%)
Kidney disease	Not reported	20/153 (13%)	187 (13%)
Elevated Creatinine* *Missing*	Not reported	-	395/1399 (28%) *39 (3%)*
Abnormal chest imaging findings	Not reported	-	1233 (86%)
ICU entry	Not reported		184 (13%)
AST > 40 U/L *Missing*	Not reported	-	667/1303 (51%) *135 (9%)*
ALT > 40 U/L *Missing*	Not reported	-	423/1305 (32%) *133 (9%)*

CHF: congestive heart failure, *Elevated creatinine:>1.2 mg/dl for females, >1.4 mg/dl for male; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Insufficient control of geographical and temporal variations of COVID-19 hospital care

The study consists of data collected, globally, from different types of hospitals (urban and rural, academic and community, for-profit and non-profit hospitals), over a four-to-five-month period since the first COVID-19 case cluster was reported in China. The pandemic peaked in different geographic areas at different times, and the management of COVID-19 evolved rapidly as experience and clinical data emerged. Therefore, the volume and the severity of the COVID-19 cases that presented at hospitals, as well as, the care provided, including the suggested or preferred COVID-19 treatment(s) would differ geographically over time depending on factors such as the cumulative understanding of the disease, the experiences of the providers with COVID-19 patients and the medical resources available to hospitals for managing COVID-19 patients, etc.

[e] https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm

The study did not sufficiently account for these potential temporal variations in hospitalized cases and clinical practices in their analyses, because none of their analyses adjusted for calendar time. Although they conducted individual analyses on effectiveness outcome (mortality) by continent of origin, that was still likely insufficient to account for the variations of COVID-19 case severity and the clinical care provided in the 671 hospitals that contributed data. The author did not report the findings of the analyses on safety outcome (ventricular arrhythmia) by country of origin.

Additionally, the author did not provide the distribution of the types of hospitals that contributed data by treatment groups or describe the calendar time of index date by treatment groups. Therefore, it is difficult to evaluate how the geographical variability or temporal changes in case or treatment patterns might impact the observed outcome risk. The author also did not report the characteristics for the reference group in the analyses stratified by continent of origin. Given the regional differences and temporal changes in practice, it is still difficult to interpret the relative effectiveness or safety findings of the study, given that reference group was still poorly defined.

Concerns on the choice of index time and immortal time

As most of the previous studies that evaluated hydroxychloroquine or chloroquine treatment in COVID-19 population, this study set the index time for the analyses at hospital admission, which results in immortal time bias and insufficient control of disease severity at treatment initiation. The study also excluded patients who received treatment starting more than 48 hours after COVID-19 diagnosis, which reduced the "immortal time" in the treated group, but that did not completely eliminate immortal time bias.

Additionally, the author restricted the analysis to only patients who received hydroxychloroquine or chloroquine treatments within 48 hours of hospital admission might create or worsen confounding by disease severity. Patients treated with the study drugs likely represent those with the most severe disease that need treatment at the time of, or shortly after hospital admission.

Although the study was able to adjust for some covariates (i.e. quick sepsis-related organ failure assessment [qSOFA]) at treatment initiation, the author did not provide clear description on the assessment windows of most covariates, including oxygen saturation on room air, use of antiviral therapy or cardiac medication, the index time issue would still lead to insufficient control of the differences in COVID-19 disease severity or underlying cardiac risk.

Other methodologic concerns

The study ascertained information on cardiac medications (angiotensin converting enzyme [ACEi] inhibitors, angiotensin receptor blockers, and statins) and antiviral therapy (other than the hydroxychloroquine, chloroquine or redemsivir) at *baseline*, but never defined "baseline". It only mentioned that the index date for the COX regression analyses was set at "hospital admission". However, the "baseline" antiviral therapy use was ~40% in the study population as treatment for COVID-19, the most common were lopinavir with ritonavir (31·6%), ribavirin (20·3%), and oseltamivir (13·1%), and combination therapy with more than one of these antiviral regimens was used in 17·4% of patients. It seems unlikely that outpatient antiviral therapy for COVID-19 disease would be so prevalent at the time of COVID-19 hospital admission.

It also could be problematic if the study data source captured remote usage of cardiac or antiviral medications, because those medications might not be continuously used at the time of hospitalization for COVID-19.

While the authors provided some information on other antiviral therapy and cardiac medications, they did not report the information by treatment groups.

The findings on increased risk of safety outcome (ventricular arrythmia) associated with the hydroxychloroquine or chloroquine, with or without arrhythmia, is consistent with biological plausibility. However, the author did not clearly describe how they identified the safety outcome from the source data, nor provided data to support the validity of the outcome events. The observed cardiac risk associated with hydroxychloroquine or chloroquine could be biased because the cardiac adverse events could be monitored more closely in the treated group given the known risk, or they could more likely be captured due to continuous monitoring among patients with more severe disease in an ICU or a higher acuity of care. Additionally, death due to cardiac arrest was not included as a safety outcome. This outcome misclassification would lead to underestimation of absolute risk and under- or over-estimation of relative risk. Since the index time for the analyses was set at hospital admission, some of the ventricular arrythmia events might have occurred before the treatment initiation.

Lastly, although the study collected data from six continents, the generalizability of the study findings might not be applicable outside of the hospitals that contributed the data. In addition, the results would only apply to patients who received hydroxychloroquine or chloroquine treatment within 48 hours after COVID-19 diagnosis and to those who were not on mechanical ventilation when treatment was initiated.

Conclusions

The limitations of the Mehra study make it difficult to interpret the findings on the effectiveness or safety of hydroxychloroquine or chloroquine, with or without macrolide, despite the biological plausibility of the safety signal for increased ventricular arrhythmia risk with these exposures.

The potential biases introduced could lead to either under- or over-estimation of the observed effectiveness and safety.

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