Global HCQ/CQ studies

October 25, 2020
@CovidAnalysis

Early treatment ↓64%

100% of early treatment studies are positive. 64% is the median improvement.

Late treatment ↓24%

63% of late treatment studies are positive.

150 HCQ studies
88 peer reviewed

Early treatment of COVID-19 with HCQ shows high efficacy

10/24 **Positive**

Pre-Exposure Prophylaxis study

***Goenka** et al., SSRN, doi:10.2139/ssrn.3689618 (Preprint)*

Seroprevalence of COVID-19 Amongst Health Care Workers in a Tertiary Care Hospital of a Metropolitan City from India

Study of SARS-CoV-2-IgG antibodies in 1122 health care workers in India finding 87% lower positives for adequate HCQ prophylaxis, 1.3% HCQ versus 12.3% for no HCQ prophylaxis.

Adequate prophylaxis is defined as 400mg 1/wk for >6 weeks.

IgG positive, ↓87.2%, p=0.03
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

10/24 **Negative**

Post Exposure Prophylaxis study

***Barnabas** et al., IDWeek (Preprint)*

Hydroxychloroquine for Post-exposure Prophylaxis to Prevent Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Trial

Early terminated PEP RCT comparing HCQ and vitamin C with 781 patients (83% household contacts), reporting no significant differences.

The study enrolled people with their last exposure within 4 days, i.e., if someone was exposed for 30 days in a row, they could be enrolled anywhere from day 1 to day 34. Therefore many were likely infected earlier than the enrollment date. Note that PCR has a very high false negative rates, e.g., 100% on day 1 and 67% on day 4 here [1].

50% of infections were detected by day 4. With the PCR false negatives and treatment delays it is likely that a majority of infections happened before enrollment or before HCQ can reach therapeutic levels.

Therapy started one day after enrollment and study supplies were sent to the participant "either by courier or mail". So the arrival time of the medication is not specified. In Boulware et al., the shipping delay was up to 3.5 days, if the delay is similar here the overall delays may be:

time since first exposure - unlimited
time to enrollment - up to 4 days
time to telehealth meeting - 1 day (3 days if Friday enrollment?)
time to receive medication - up to 3.5 days

Currently only cherry-picked results have been reported - 14 day PCR+ and PCR+ symptomatic. The study uses a low and slow dosage regimen, therapeutic levels may only be reached nearer to day 14, if at all, so day 28 results should be more informative when available.

Endpoints were:

Primary outcomes:
PCR+ @28 days - NOT REPORTED YET
PCR+ @14 days - aHR 0.99 [0.64-1.52]

Seconday outcomes:
PCR+ symptomatic @28 days - NOT REPORTED YET
duration of shedding - NOT REPORTED YET

Not in study protocol:
PCR+ symptomatic @14 days - aHR 1.23 [0.76-1.99]

Dose in first 24 hours - 0.8g (compare with Boulware et al. 2g)
Dose in first 5 days - 1.6g (compare with Boulware et al. 3.8g)

Other research suggests vitamin C may be beneficial for COVID-19, e.g. [2]. No information on severity is provided - binary PCR does not distinguish replication-competence. There was 2 COVID-19 hospitalizations but the group(s) have not been reported yet.

Side effects were similar for HCQ and placebo. 84% medication adherence at day 14.

NCT04328961 [3]

Primary Outcome Measures :

1. Polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection [Time Frame: Day 1 through Day 14 after enrolment]
   Polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection from self-collected samples collected daily for 14 days
2. Polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection [Time Frame: Day 28 after enrolment]
   Polymerase chain reaction (PCR) confirmed SARS-CoV-2 infection from self-collected samples collected at study exit

Secondary Outcome Measures :

1. Rate of participant-reported adverse events [Time Frame: 28 days from start of Hydroxychloroquine therapy]
   Safety and tolerability of Hydroxychloroquine as SARS-CoV-2 PEP in adults
2. Incidence rates of COVID-19 through study completion [Time Frame: 28 days from enrolment]
   PCR-confirmed COVID-19 diagnosis

[1] ncbi.nlm.nih.gov/pmc/articles/PMC7240870/
[2] researchsquare.com/article/rs-52778/v2
[3] clinicaltrials.gov/ct2/show/NCT04328961

COVID-19 case, ↑**23.0%**, p=0.40, day 14 symptomatic PCR+
COVID-19 case, ↓**1.0%**, p=0.95, day 14 PCR+

Source Study Page Submit Corrections or Comments

10/21 **Inconc.**

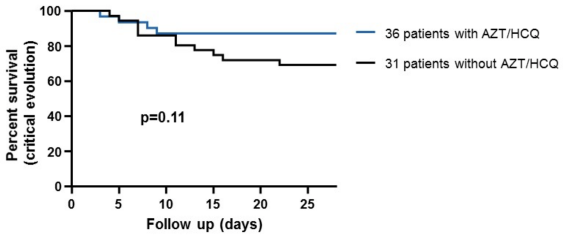
Late treatment study

Lano et al., Clinical Kidney Journal, 13:5, October 2020, 878–888, doi:10.1093/ckj/sfaa199 (Peer Reviewed)

Risk factors for severity of COVID-19 in chronic dialysis patients from a multicentre French cohort

33% lower mortality with HCQ+AZ, *p*=0.28. Retrospective 122 French dialysis patients.

69% lower combined mortality/ICU, *p*=0.11, for the subgroup not requiring O2 on diagnosis (slightly earlier treatment).



death, ↓**33.1%**, p=0.28
combined death/ICU, ↓**38.9%**, p=0.23
combined death/ICU, ↓**68.7%**, p=0.11, not requiring O2 on diagnosis
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

10/21 Inconc.

Late treatment study

Dubee *et al., medRxiv, doi:10.1101/2020.10.19.20214940 (Preprint)*

A placebo-controlled double blind trial of hydroxychloroquine in mild-to-moderate COVID-19

Small early terminated late stage (60% on oxygen) RCT in France showing 46% lower mortality (~**423,318** potential lives saved with global HCQ).

mortality at 28 days relative risk RR 0.54 [0.21-1.42]
combined mortality/intubation at 28 days relative risk RR 0.74 [0.33-1.70]

If not stopped early and the same trend continued, statistical significance would be reached on 28 day mortality after ~550 patients (1,300 patients were planned).

Mortality results are not provided for subgroups. For the subgroups receiving AZ:

HCQ+(AZ from day 0): combined mortailty/intubation RR 0.16, *p* = 0.21
(0/10 HCQ+AZ and 3/11 placebo, 0.5 added for calculations due to 0)
HCQ+(AZ later), combined mortality/intubation RR 0.42 [0.05-3.54]

No safety concerns were identified.

NCT04325893

Table 2: Outcomes in the intention-to-treat population

Outcomes	All patients (N = 247)	Hydroxychloroquine (N = 124)	Placebo (N = 123)	Relative risk (95% CI)
Primary outcome				
Day 14	17 (6.9)	9 (7.3)	8 (6.5)	1.12 (0.45–2.80)
Day 28	21 (8.5)	9 (7.3)	12 (9.8)	0.74 (0.33–1.70)
Mortality				
Day 14	12 (4.9)	6 (4.8)	6 (4.9)	0.99 (0.33–2.99)
Day 28	17 (6.9)	6 (4.8)	11 (8.9)	0.54 (0.21–1.42)

death, ↓**46.0%**, p=0.21, mortality at day 28
combined intubation/death, ↓**26.0%**, p=0.82, combined mortality/intubation at day 28
death, ↓**84.4%**, p=0.21, HCQ+AZ from day 0 subgroup combined mortality/intubation

Source Study Page Submit Corrections or Comments

10/21 **Positive**

Late treatment study

Ñamendys-Silva *et al., Heart & Lung, doi:10.1016/j.hrtlng.2020.10.013 (Peer Reviewed)*

Outcomes of patients with COVID-19 in the Intensive Care Unit in Mexico: A multicenter observational study

Retrospective 164 ICU patients in Mexico showing 32% lower mortality with HCQ+AZ and with 37% lower with CQ.

HCQ+AZ vs. neither HCQ or CQ relative risk RR 0.68, p = 0.03
CQ vs. neither HCQ or CQ relative risk RR 0.63, p = 0.02
HCQ+AZ or CQ vs. neither relative risk RR 0.65, p = 0.006

death, ↓**32.3%**, p=0.18, HCQ+AZ vs. neither HCQ or CQ
death, ↓**37.1%**, p=0.09, CQ vs. neither HCQ or CQ
death, ↓**34.5%**, p=0.006, HCQ+AZ or CQ

Source Study Page Submit Corrections or Comments

10/20 **Meta**

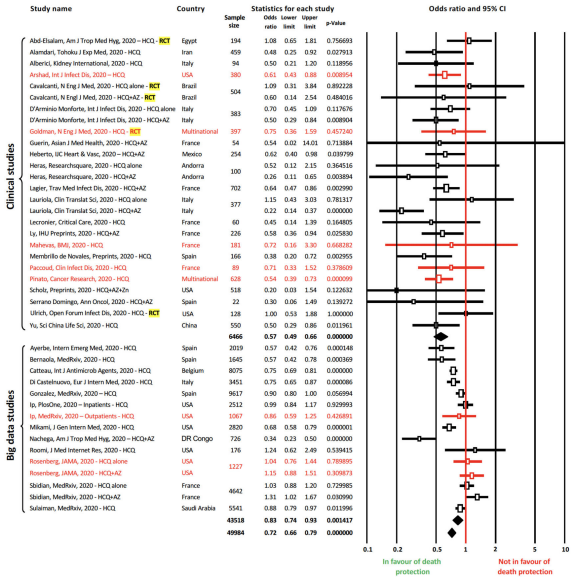
Early, Late

IHU Marseille *(Preprint) (meta analysis - not included in study count)*

Meta-analysis on chloroquine derivatives and COVID-19 mortality

Updated meta analysis of 41 studies showing CQ/HCQ OR 0.57, p<0.0001 from clinical studies (~**395,710** potential lives saved with global HCQ).

For big data studies authors find inconsistent results and OR 0.83, p=0.0014, and for all studies combined OR 0.72, p<0.0001.



Source Study Page Submit Corrections or Comments

10/20 **Negative**

Late treatment study

Solh *et al., medRxiv, doi:10.1101/2020.10.16.20214130 (Preprint)*

Clinical course and outcome of COVID-19 acute respiratory distress syndrome: data

from a national repository

Retrospective database analysis of 7,816 Veterans Affairs hospitalized patients analyzing progression to ARDS and 30-day mortality from ARDS. Confounding by indication is likely. Chronological bias is likely, with HCQ more likely to be used earlier on, before significant improvements in overall treatment.

No results are provided for HCQ for progression to ARDS.

death, ↑**18.0%**, p=0.17

Source Study Page Submit Corrections or Comments

10/17 **Safety**

Early treatment study

Mohana et al., International Journal of Infectious Diseases, doi:10.1016/j.ijid.2020.10.031 (preprint 8/17) (Peer Reviewed) (not included in the study count)

Hydroxychloroquine Safety Outcome within Approved Therapeutic Protocol for COVID-19 Outpatients in Saudi Arabia

Safety study of 2,733 patients in Saudi Arabia showing HCQ in mild to moderate cases in an outpatient setting, within the protocol recommendation and inclusion/exclusion criteria, is safe, highly tolerable, and has minimal side effects. No ICU admission or deaths were reported.

Source Study Page Submit Corrections or Comments

10/15 **Positive**

Late treatment study

Guisado-Vasco (Peer Reviewed)

Clinical characteristics and outcomes among hospitalized adults with severe COVID-19 admitted to a tertiary medical center and receiving antiviral, antimalarials, glucocorticoids, or immunomodulation with tocilizumab or cyclosporine: A retrospective observational study (COQUIMA cohort)

Retrospective 607 patients reporting results for early outpatient HCQ use with mortality odds ratio OR 0.092 [0.022-0.381], p = 0.001 (65 patients), and for hospital use, mortality odds ratio OR 0.737 [0.38-1.41], p = 0.36 (558 patients). Median age 69.

	OR (95% CI)	p-value
Gender (female)	0·769 (0·512 - 1·153)	**0·203**
Age, yrs	**1·097 (1·075 - 1·119)**	**<0·001**
Chest X-ray score at admission	**1·299 (1·155 - 1·461)**	**<0·001**
Invasive mechanical ventilation	**4·347 (2·338 - 8·081)**	**<0·001**
Hydroxychloroquine - previous to admission	**0·092 (0·022 - 0·381)**	**0·001**
Hydroxychloroquine therapy	0·737 (0·384 - 1·412)	**0·357**

death, ↓**20.3%**, p=0.36
death, ↓**88.0%**, p=0.001, outpatient use
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

10/15 **Negative**

Late treatment study

SOLIDARITY *Trial Consortium, medRxiv, doi:10.1101/2020.10.15.20209817 (Preprint)*

Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results

WHO SOLIDARITY open-label trial with 954 very late stage (64% on oxygen/ventilation) HCQ patients, mortality relative risk RR 1.19 [0.89-1.59], *p*=0.23.

HCQ dosage very high as in RECOVERY, 1.6g in the first 24 hours, 9.6g total over 10 days, only 25% less than the high dosage that Borba et al. show greatly increases risk (OR 2.8) [1].

Authors state they do not know the weight or obesity status of patients to analyze toxicity (since they do not adjust dosage based on patient weight, toxicity may be higher in patients of lower weight).

KM curves show a spike in HCQ mortality days 5-7, corresponding to ~90% of the total excess seen at day 28 (a similar spike is seen in the RECOVERY trial).

Almost all excess mortality is from ventilated patients.

Authors refer to a lack of excess mortality in the first few days to suggest a lack of toxicity, but they are ignoring the very long half-life of HCQ and the dosing regimen - much higher levels of HCQ will be reached later. Increased mortality in Borba et al. occurred after 2 days.

An unspecified percentage used the more toxic CQ. No placebo used.

[1] c19study.com/borba.html

death, ↑**19.0%**, p=0.23

Source Study Page Submit Corrections or Comments

10/12 **Inconc.**

Late treatment study

Annie *et al., Pharmacotherapy, doi:10.1002/phar.2467 (Peer Reviewed)*

Hydroxychloroquine in hospitalized COVID-19 patients: Real world experience assessing mortality

Retrospective database analysis with PSM not including COVID-19 severity, finding

mortality OR 0.95 [0.62-1.46] for HCQ, and 1.24 [0.70-2.22] for HCQ+AZ. Confounding by indication likely.

death, ↓**4.3%**, p=0.83
death, ↑**20.5%**, p=0.46
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

10/11 **Inconc.**

Late treatment study

Sili et al., medRxiv, doi:10.1101/2020.10.09.20209775 (Preprint) (not included in the study count)

Factors associated with progression to critical illness in 28 days among COVID-19 patients: results from a tertiary care hospital in Istanbul, Turkey

Analysis of hospitalized patients in Turkey showing HCQ was given to 99.2% of patients and the incidence of critical illness was lower than most studies. Authors note "whether HCQ administration lowered the rates of critical illness development is beyond the scope of this study." There is no comparison with a control group.

Source Study Page Submit Corrections or Comments

10/8 **Positive**

Late treatment study

Aparisi et al., medRxiv, doi:10.1101/2020.10.06.20207092 (Preprint)

Low-density lipoprotein cholesterol levels are associated with poor clinical outcomes in COVID-19

Retrospective 654 hospitalized patients focused on low-density lipoprotein cholesterol levels, also showing results for HCQ with 605 HCQ patients, unadjusted 30 day mortality relative risk RR 0.37, p = 0.008.

Variable	All population N= 654	Survivors N= 505 (77.2%)	Non-survivors N= 149 (22.8%)	p-value
Azithromycin (%)	588 (94.2%)	470 (95.3%)	118 (90.1%)	**0.022**
Betaferon (%)	244 (39.1%)	182 (36.9%)	62 (47.3%)	**0.03**
Hydroxychloroquine (%)	605 (97%)	483 (98%)	122 (93.1%)	**0.008**
Lopinavir/Ritonavir (%)	590 (94.4%)	473 (95.7%)	117 (89.3%)	**0.004**

death, ↓**63.0%**, p=0.008

Source Study Page Submit Corrections or Comments

10/8 **Negative**

Late treatment study

Soto-Becerra et al., medRxiv, doi:10.1101/2020.10.06.20208066 (Preprint)

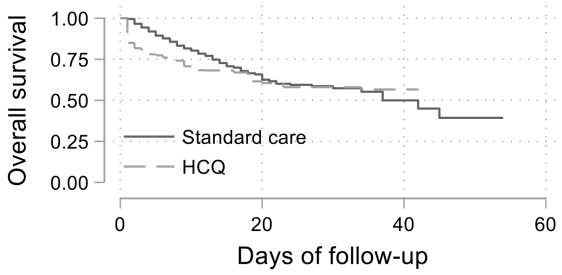
Real-World Effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: Results of a target trial emulation using observational data from a nationwide Healthcare System in Peru

Retrospective database study of 5683 patients, 692 received HCQ/CQ+AZ, 200 received HCQ/CQ, 203 received ivermectin, 1600 received AZ, 358 received ivermectin+AZ, and 2630 received standard of care.

HCQ+AZ was associated with 84% higher all-cause mortality compared to standard care, aHR = 1.84 [1.12-3.02]. Substantial confounding by indication is likely, with more serious cases more likely to receive treatment. Substantial increased treatment mortality is seen, independent of the actual treatment used. KM curves also agree with this, showing increased mortality early on, with very high mortality on day 2, but every treatment did better than standard of care at the latest available date.

Authors use a machine learning based propensity scoring system that appears over-parameterized and likely to result in significant overfitting and inaccurate results. Essentially they test for all interactions between two and three covariates. The nature and large number of covariates means many random correlations may be found. COVID-19 severity is not used.

See also: [1].



[1] twitter.com/Covid19Crusher/status/1315461049034907650

death, ↑**84.0%**, p=0.02

Source Study Page Submit Corrections or Comments

10/6 **Inconc.**

Late treatment study

DISCOVERY Trial (Preprint)

DISCOVERY Trial Preliminary Results

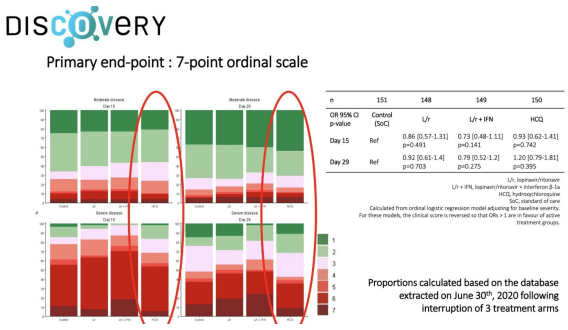
Early terminated DISCOVERY trial shows improvements in mortality and day 29 7-point ordinal scale with HCQ.

Mortality improvements are seen at both day 15 and day 29 in the graph. Details are not given but based on measuring the pixels on the graph, we estimate 13/150 treatment deaths and 19/151 control deaths, RR 0.69, p=0.35. If this trend continues, statistical significance will be reached after about 1,000 patients (3,100 patients were planned but the interim results have only 150 HCQ and 151 control patients).

7-point scale OR 0.83 [0.55-1.27], p = 0.395, not statistically significant with the small number of patients.

Trial details: [1]. Results are reported with OR>1 favoring treatment, we have converted to OR<1 favoring treatment.

Compared to RECOVERY and SOLIDARITY, the dosage used here is much lower.



[1] clinicaltrials.gov/ct2/show/NCT04315948

death, ↓**31.1%**, p=0.35, 29 day mortality estimated from graph
7-point scale status, ↓**17.0%**, p=0.40

Source Study Page Submit Corrections or Comments

Early, Late

Prodromos et al., New Microbes and New Infections, doi:10.1016/j.nmni.2020.100776 (Peer Reviewed) (meta analysis - not included in study count)

10/5 **Meta**

Hydroxychloroquine is effective, and consistently so used early, for Covid-19: A systematic review

Meta analysis of 43 studies: "HCQ was found consistently effective against COVID-19 when used early, in the outpatient setting. It was found overall effective also including inpatient studies. No unbiased study found worse outcomes with HCQ use. No mortality or serious safety adverse event was found.

Source Study Page Submit Corrections or Comments

10/2 **Positive**

Late treatment study

Nachega et al., The American Journal of Tropical Medicine and Hygiene, doi:10.4269/ajtmh.20-1240 (Peer Reviewed)

Clinical Characteristics and Outcomes of Patients Hospitalized for COVID-19 in Africa: Early Insights from the Democratic Republic of the Congo

Retrospective 766 hospitalized patients in DRC showing mortality reduced from 29% to 11%, and improvement at 30 days increased from 65% to 84%.

Mortality cox regression adjusted hazard ratio aHR 0.26, $p < 0.001$
Risk of no improvement adjusted odds ratio aOR 0.28, $p < 0.001$

Using marginal structural model analysis these risks became:

Mortality MSM adjusted odds ratio aOR 0.65, $p = 0.166$
Risk of no improvement MSM adjusted odds ratio aOR = 0.65, $p = 0.132$

Median age 46, 630 treated with CQ+AZ.

TABLE 3
Cox regression of factors associated with hazard of death (*N* = 766)

Characteristic	Died, *n* (%)	Unadjusted hazards ratio (95% CI)	Adjusted hazards ratio (95% CI)*	*P*-value
Chloroquine/azithromycin–based treatment				
No (*n* = 96)	28 (29.2)	1	1	–
Yes (*n* = 630)	69 (11.0)	0.33 (0.21–0.52)	0.26 (0.16–0.42)	< 0.001

death, ↓**27.6%**, p=0.17
no improvement, ↓**25.8%**, p=0.13
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

10/1 **Positive**

Late treatment study

Almazrou et al., Saudi Pharmaceutical Journal, doi:10.1016/j.jsps.2020.09.019 (Peer Reviewed)

Comparing the impact of Hydroxychloroquine based regimens and standard treatment on COVID-19 patient outcomes: A retrospective cohort study

Retrospective 161 hospitalized patients in Saudi Arabia showing lower ventilation and ICU admission with HCQ, but not statistically significant with the small sample sizes.

ventilation, ↓**65.0%**, p=0.16
ICU admission, ↓**21.0%**, p=0.78

Source Study Page Submit Corrections or Comments

10/1 **Meta**

PrEP, PEP

Garcia-Albeniz et al., medRxiv, doi:10.1101/2020.09.29.20203869 (Preprint) (meta

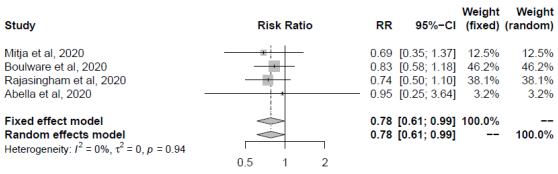
analysis - not included in study count)

Brief communication: A meta-analysis of randomized trials of hydroxychloroquine for the prevention of COVID-19

Combination of the four underpowered prophylaxis RCTs to date showing statistically significant results, RR 0.78 [0.61-0.99].

The actual effect of HCQ is likely to be higher for several reasons: the trials did not adjust for losses to follow-up or other deviations from protocol. There was very long treatment delays in the postexposure prophylaxis trials - in one trial, about a third of participants were enrolled 4 days after exposure with an additional shipping delay of ~46 hours on average, in the other, participants were enrolled up to 7 days after exposure, with an unknown additional delay before treatment, and results suggesting that exposure detection was delayed.

For other reasons see: [1, 2, 3, 4].



[1] c19study.com/boulware.html
[2] c19study.com/mitjapep.html
[3] c19study.com/rajasingham.html
[4] c19study.com/abella.html

COVID-19 case, ↓**22.0%**, p=0.04

Source Study Page Submit Corrections or Comments

9/30 **Positive**

Post Exposure Prophylaxis study

***Polat** et al., Medical Journal of Bakirkoy, 16:3, 280-6, doi:10.5222/BMJ.2020.50469 (Peer Reviewed)*

Hydroxychloroquine Use on Healthcare Workers Exposed to COVID-19 -A Pandemic Hospital Experience

Small prophylaxis study of 208 healthcare workers in Turkey, 138 with high risk exposure received HCQ, while 70 with low and medium risk exposure did not. COVID-19 cases were lower in the treatment group, relative risk RR 0.43, p = 0.026. Since the control group had lower risk, the actual benefit may be larger.

COVID-19 case, ↓**57.0%**, p=0.03

Source Study Page Submit Corrections or Comments

Late treatment study

Ayerbe et al., Internal and Emergency Medicine, doi:0.1007/s11739-020-02505-x (Peer Reviewed)

The association of treatment with hydroxychloroquine and hospital mortality in COVID-19 patients

2075 hospital patients in Spain showing HCQ reduces mortality 52%, odds ratio OR 0.39, *p*<0.001, after adjustment for age, gender, temperature > 37 °C, and saturation of oxygen < 90% treatment with azithromycin, steroids, heparin, tocilizumab, a combination of lopinavir with ritonavir, and oseltamivir, and date of admission (model 4).

	Mortality odds ratio (95% CI)	*p* value
Model 1	0.44 (0.29–0.67)	< 0.001
Model 2	0.45 (0.30–0.68)	< 0.001
Model 3	0.39 (0.24–0.64)	< 0.001
Model 3 with a statistical interaction term for HCQ and azithromycin		
1 Main effect HCQ	0.56(0.34–0.92)	0.022
2 Main effect azithromycin	0.53(0.19–1.50)	0.233
3 Interaction (1 and 2)	1.11(0.38–3.29)	0.846
Model 4	0.39 (0.24–0.64)	< 0.001

Model 1 Adjusted for age and gender

Model 2 Adjusted for age, gender, temperature > 37 °C, and saturation of oxygen < 90%

Model 3 Adjusted for age, gender, temperature > 37 °C, and saturation of oxygen < 90% treatment with azithromycin, steroids, heparin, tocilizumab, a combination of lopinavir with ritonavir, and oseltamivir

Model 4 Adjusted for age, gender, temperature > 37 °C, and saturation of oxygen < 90% treatment with azithromycin, steroids, heparin, tocilizumab, a combination of lopinavir with ritonavir, and oseltamivir, and date of admission

9/30 **Positive**

death, ↓52.2%, p<0.001
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

9/30 **Meta**

PrEP, PEP, Early

Ladapo et al., medRxiv, doi:10.1101/2020.09.30.20204693 (Preprint) (meta analysis - not included in study count)

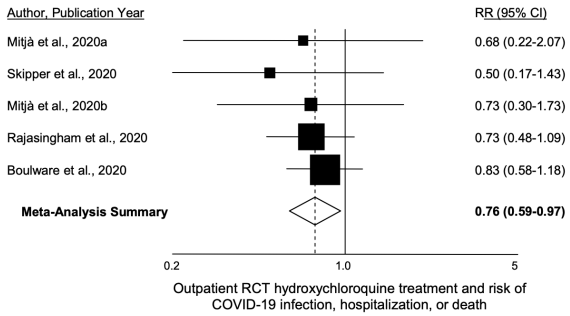
Randomized Controlled Trials of Early Ambulatory Hydroxychloroquine in the Prevention of COVID-19 Infection, Hospitalization, and Death: Meta-Analysis

Meta analysis of prophylactic and early treatment RCTs, 24% reduction in cases, hospitalization or death with HCQ, RR 0.76, *p*=0.025. No serious adverse cardiac events were reported. 5,577 patients.

The Boulware study provides a breakdown for treatment delay. For the case of < ~4 days (2 days enrollment, ~46 hours shipping), the result of the meta analysis becomes RR 0.68, *p*=0.0097.

The actual effect may be larger due to treatment delays, followup loss, protocol deviation, active placebos, no severity analysis for cases, and suboptimal regimens.

For the individual studies see [1, 2, 3, 4, 5].



[1] c19study.com/boulware.html
[2] c19study.com/mitjapep.html
[3] c19study.com/rajasingham.html
[4] c19study.com/skipper.html
[5] c19study.com/mitja.html

combined cases/death/hospitalization, ↓**24.0%**, p=0.03

Source Study Page Submit Corrections or Comments

9/30 **Inconc.**

Pre-Exposure Prophylaxis study

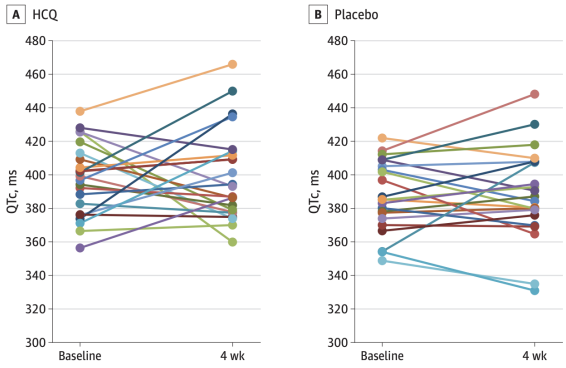
***Abella** et al., JAMA Internal Medicine, doi:doi:10.1001/jamainternmed.2020.6319 (Peer Reviewed)*

Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers

Very small early-terminated underpowered PrEP RCT with 64/61 HCQ/control patients and only 8 infections, HCQ infection rate 6.3% versus control 6.6%, RR 0.95 [0.25 - 3.64].

There was no hospitalization or death, no significant difference in QTc, no severe adverse events, no cardiac events (e.g., syncope and arrhythmias) observed. Medication adherence was 81%. Therapeutic levels of HCQ may not have been reached by the time of the infection in the first week.

2 infections were reported to be after discontinuation of the medication, but the authors do not specify which arm these were in. Hypothetically, if these were both in the HCQ arm, the resulting RR for treatment would be much lower.



COVID-19 case, ↓**5.0%**, p=1.00

Source Study Page Submit Corrections or Comments

9/29 **Positive**

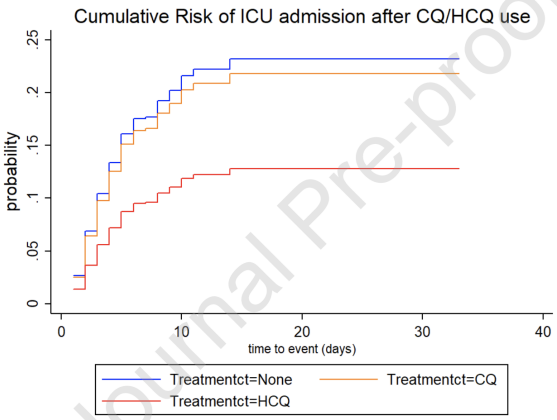
Late treatment study

***Lammers** et al., Int. J. Infectious Diseases, doi:10.1016/j.ijid.2020.09.1460 (Peer Reviewed)*

Observational study 1,064 hospitalized patients in the Netherlands, 53% reduced risk of transfer to the ICU for mechanical ventilation with HCQ treatment starting on the first day of admission.

Weighted propensity score adjusted hazard ratio for transfer to the ICU with HCQ treatment, HR = 0.47, p = 0.008. For CQ, HR = 0.8, p = 0.207. Mortality results in this study are only for mortality before transfer to the ICU. The combined ICU/death HR was 0.68, p = 0.024 for HCQ, and 0.85, p = 0.224 for CQ.

Observational, multicenter, cohort study of hospitalized COVID-19 patients. 189 HCQ patients, 377 CQ, 498 control.



combined death/ICU, ↓**32.0%**, p=0.02

Source Study Page Submit Corrections or Comments

9/29 **Inconc.**

Late treatment study

Dabbous *et al., Research Square, doi:10.21203/rs.3.rs-83677/v1 (Preprint)*

A Randomized Controlled Study Of Favipiravir Vs Hydroxychloroquine In COVID-19 Management: What Have We Learned So Far?

Small RCT comparing HCQ and favipiravir, with 50 patients in each arm, finding that 55.1% of HCQ patients were PCR negative on day 7 compared to 48% for favipiravir, *p* = 0.7. There was no comparison with a control group.

Source Study Page Submit Corrections or Comments

9/28 **Meta**

Post Exposure Prophylaxis study

Luco*, J., ResearchGate, doi:10.13140/RG.2.2.24214.98880 (Preprint) (meta analysis - not included in study count)*

Hydroxychloroquine as Post-Exposure Prophylaxis for Covid-19: Why simple data analysis can lead to the wrong conclusions from well-designed studies

Reanalysis of Boulware et al. PEP trial data showing statistically significant improvements with HCQ.

Source Study Page Submit Corrections or Comments

9/27 **Meta**

Post Exposure Prophylaxis study

Wiseman et al., medRxiv, doi:10.1101/2020.08.19.20178376 (Preprint) (meta analysis - not included in study count)

Treatment and prevention of early disease before and after exposure to COVID-19 using hydroxychloroquine: A protocol for exploratory re-analysis of age and time

Analysis of Boulware et al. data showing 65% reduction in cases for treatment within 3 days, RR 0.35, *p*=0.044.

Authors were able to obtain data on the shipping delay for participants which adds up to 3.5 days to the treatment time, so for example some "day 1" participants may actually have started treatment 4 days after reported exposure.

Restratifying shows a 65% reduction in COVID-19 when the medication was received within 3 days of the reported exposure. Authors have requested further data to improve accuracy on the time medication was received which may reduce the confidence interval.

Table 3: Effect of hydroxychloroquine on post-exposure development of COVID-19, interim estimate based on new data supplied for enrollment to delivery

Exposure – receipt	%pos-HCQ	%posPlac	Risk Ratio*	95% CI
0-3 days	5.4	15.7	0.35	0.13 – 0.93 (p=0.043, Fisher's test)
3-4 days	12.4	15.3	0.81	0.4 – 1.6
4-5 days	12.7	14.9	0.86	0.45 – 1.6
5-7 days	15.7	11.4	1.4	0.69 – 2.7

Interim estimate based on additional data provided by Dr. Boulware regarding time from enrollment to drug receipt (time of first dose is unknown). Not accounting for enrollment time, the exposure-receipt time may vary ± 24 hours. These estimates do not account for time zone differences, but include a nominal 6-hour same day delivery time for Canadian subjects. n = number of subjects in each time stratum for HCQ of Placebo.

COVID-19 case, **↓65.0%**, p=0.04

Source Study Page Submit Corrections or Comments

Early, Late

Gasperetti et al., EP Europace, doi:10.1093/europace/euaa216 (Peer Reviewed) (not included in the study count)

Arrhythmic safety of hydroxychloroquine in COVID-19 patients from different clinical settings

9/24 **Safety**

Safety study of 649 patients finding that HCQ administration is safe for short-term treatment for patients with COVID-19 infection regardless of the clinical setting of delivery, causing only modest QTc prolongation and no directly attributable arrhythmic deaths.

Arrhythmic safety data from a large cohort of patients treated with HCQ alone or in combination with other QT-prolonging drugs.

Source Study Page Submit Corrections or Comments

9/24 **Positive**

Late treatment study

Shoaibi et al., medRxiv, doi:10.1101/2020.09.23.20199463 (Preprint)

Comparative Effectiveness of Famotidine in Hospitalized COVID-19 Patients

Retrospective database analysis focused on Famotidine but also showing results for HCQ users, with unadjusted mortality RR 0.85, p<0.001 (13.6% vs. 16.1%).

death, ↓15.4%, p<0.001

Source Study Page Submit Corrections or Comments

9/23 **Negative**

Late treatment study

Ulrich et al., Open Forum Infectious Diseases, doi:10.1093/ofid/ofaa446 (Peer Reviewed)

Treating Covid-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind, Randomized Controlled Trial in Hospitalized Patients

Small RCT on very late stage use of HCQ, with 48% on oxygen at baseline. 67 HCQ patients, 61 control.

Baseline states were not comparable - 82% more HCQ patients had the highest severity at baseline, there was 32% more male HCQ patients, and 44% more control patients used AZ. The HCQ group also had significantly more patients with cerebrovascular disease, cardiovascular disease (non-hypertension), renal disease (non-dialysis), and a history of organ transplants.

30 day mortality RR 1.06, p = 1.0.

	Overall N = 128	HCQ N = 67	Placebo N = 61	P
COVID-19 severity score[2]				0.777
3: Hospitalized, on non-invasive ventilation or high-flow nasal cannula	21 (16.4)	14 (20.9)	7 (11.5)	
Antibacterial agents				
Azithromycin: n (%)	30 (23.4)	13 (19.4)	17 (27.9)	0.357
30-day mortality	13 (10.2)	7 (10.4)	6 (9.8)	1.000

death, ↑6.0%, p=1.00

Source Study Page Submit Corrections or Comments

9/22 **Positive**

Late treatment study

Serrano et al., Ann. Oncol., 2020, Sep, 31, S1026, doi:10.1016/j.annonc.2020.08.1830 (Peer Reviewed)

COVID-19 and lung cancer: What do we know?

Small retrospective study of 22 lung cancer patients, 14 treated with HCQ+AZ, showing HCQ+AZ mortality relative risk RR 0.57, p = 0.145.

death, ↓**43.0%**, p=0.14

Source Study Page Submit Corrections or Comments

Pre-Exposure Prophylaxis study

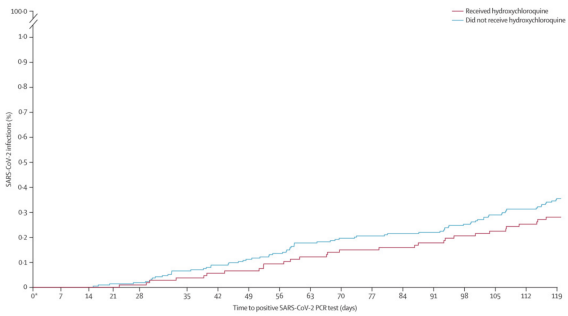
Gentry *et al., Lancet Rheumatology, doi:10.1016/S2665-9913(20)30305-2 (Peer Reviewed)*

Long-term hydroxychloroquine use in patients with rheumatic conditions and development of SARS-CoV-2 infection: a retrospective cohort study

Retrospective patients with rheumatologic conditions showing zero mortality with HC Q, odds ratio OR 0.13, p=0.10. 0 of 10,703 COVID-19 deaths for HCQ patients versus 7 of 21,406 for control patients.

COVID-19 cases OR 0.79, p=0.27. There are several significant differences in the propensity matched patients that could affect results, e.g., 20.9% SLE versus 24.7%.

9/21 **Inconc.**



death, ↓**86.7%**, p=0.10
COVID-19 case, ↓**20.9%**, p=0.27
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

9/21 **Inconc.**

Pre-Exposure Prophylaxis study

Rajasingham *et al., medRxiv, doi:10.1101/2020.09.18.20197327 (Peer Reviewed)*

Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial

PrEP RCT showing HR 0.73, p = 0.12.

Trial halted after 47% enrollment, $p < 0.05$ will be reached at ~75% enrollment if similar results continue. Trial halted due to low enrollment. US prescriptions only stopped briefly, resuming in June, so the authors can complete the study [1].

HR 0.66/0.68 for full medication adherence, 0.72/0.74, $p = 0.18/0.22$ overall (1x/2x dosing).

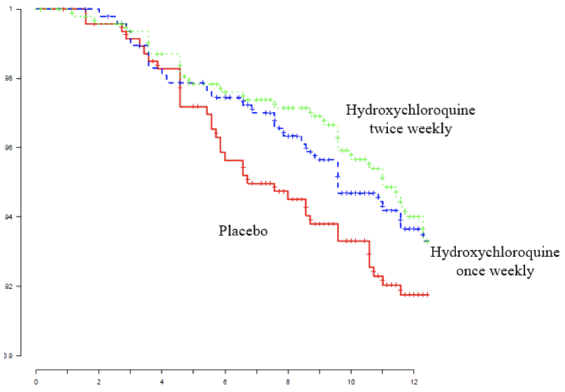
Efficacy for first responders was higher, OR 0.32, $p = 0.01$. First responders had a much higher incidence, allowing greater power, and reducing the effect of confounders such as misdiagnosis of other conditions or survey issues.

Performance is similar to placebo for the first 3 weeks. The effect may be greater with a dosage regimen that achieves therapeutic levels faster [2]. ~40% of participants suspected they might have had COVID-19 before the trial, the effect in people without prior COVID-19 may be higher.

Authors note:

- the trial was underpowered
- investigation into more frequent dosing may be warranted
- insufficient dosing with no participants achieving more than the *in vitro* EC_{50}

Internet survey RCT subject to survey bias. There was no death or ICU admission. Low risk healthcare workers, median age ~40. 494 1x/week dosing, 495 2x/week dosing, 494 control participants (1x and 2x participants received the same overall dosage).



[1] wattsupwiththat.com/2020/08/24/hydroxychloroquine-in-covid-19-treatment-act...
[2] tandfonline.com/doi/full/10.1080/00498254.2020.1824301

hospitalization, ↓**50.1%**, p=1.00
COVID-19 case, ↓**27.0%**, p=0.12

Source Study Page Submit Corrections or Comments

9/21 **Inconc.**

Pre-Exposure Prophylaxis study

		Grau-Pujol et al., Research Square, doi:10.21203/rs.3.rs-72132/v1 (Preprint) Pre-exposure prophylaxis with hydroxychloroquine for COVID-19: initial results of a double-blind, placebo-controlled randomized clinical trial Small PrEP RCT showing that PrEP with HCQ is safe at the dosage used. No deaths, hospitalizations, or serious adverse events. With only one case (in the placebo arm), efficacy was not evaluated. COVID-19 case, ↓**70.2%**, p=0.47 Source Study Page Submit Corrections or Comments
9/21	**Safety**	Early treatment study ***Lofgren** et al., medRxiv, doi:10.1101/2020.07.16.20155531 (Preprint) (not included in the study count)* Safety of Hydroxychloroquine among Outpatient Clinical Trial Participants for COVID-19 Analysis of 2,795 outpatients not showing significant safety concerns with HCQ. No deaths were related to HCQ. There was one serious event requiring hospitalization, identical to the frequency with placebo. Source Study Page Submit Corrections or Comments
9/18	**Meta**	Late treatment study ***Axfors** et al., medRxiv, doi:10.1101/2020.09.16.20194571 (Preprint) (meta analysis - not included in study count)* Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials Meta analysis assigning 87% weight to the RECOVERY trial, producing the same result. The RECOVERY trial used excessively high non-patient-customized dosage in very sick late stage patients and the result is not generalizable to typical dosage or earlier treatment. Source Study Page Submit Corrections or Comments
9/16	**Dosing**	N/A ***Karatza** et al., Xenobiotica (Peer Reviewed) (not included in the study count)*

Optimization of hydroxychloroquine dosing scheme based on COVID-19 patients' characteristics: a review of the literature and simulations

Analysis of HCQ dosing, suggesting that high initial doses followed by low and sparse doses may offer significant benefits to patients by decreasing the viral load without reaching levels considered to produce adverse effects.

For instance, the dosing scheme proposed for a 70kg adult with moderate COVID-19 symptoms would be 600mg upon diagnosis, 400mg after 12h, 300mg after 24h, 200mg after 36h, followed by 200mg BID for 4 days, followed by 200mg OD for 5 days.

Suboptimal dosing regimens that do not fully account for the long half-life of HCQ or the patient characteristics are likely contribute to either limited efficacy where therapeutic levels take too long to reach, or significant adverse effects due to excessive dosage.

Source Study Page Submit Corrections or Comments

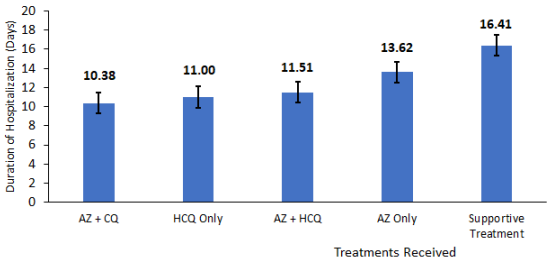
Late treatment study

Ashinyo et al., Pan African Medical Journal, 37:1, doi:10.11604/pamj.supp.2020.37.1.25718 (Peer Reviewed)

Clinical characteristics, treatment regimen and duration of hospitalization among COVID-19 patients in Ghana: a retrospective cohort study

Retrospective 307 hospital patients in Ghana showing 33% reduction in hospitalization time with HCQ, 29% reduction with HCQ+AZ, and 37% reduction with C Q+AZ.

9/15 **Positive**



AZ+CQ = azithromycin + chloroquine; HCQ = hydroxychloroquine; AZ+HCQ = Azithromycin + hydroxychloroquine; AZ = azithromycin.

hospitalization time, ↓**33.0%**, p=0.03

Source Study Page Submit Corrections or Comments

9/14 **Positive**

Late treatment study

Lauriola et al., Clinical and Translational Science, doi:10.1111/cts.12860 (Peer Reviewed)

Effect of combination therapy of hydroxychloroquine and azithromycin on mortality in COVID-19 patients

Retrospective 377 patients, 73% reduction in mortality with HCQ+AZ, adjusted hazard ratio HR 0.27 [0.17-0.41]. Mean age 71.8. No serious adverse events. Subject to incomplete adjustment for confounders.

death, ↓**73.5%**, p<0.001

Source Study Page Submit Corrections or Comments

Early treatment study

Sulaiman et al., medRxiv, doi:10.1101/2020.09.09.20184143 (Preprint)

The Effect of Early Hydroxychloroquine-based Therapy in COVID-19 Patients in Ambulatory Care Settings: A Nationwide Prospective Cohort Study

Observational prospective 5,541 patients, adjusted HCQ mortality odds ratio OR 0.36, p = 0.012. Adjusted hospitalization OR 0.57, p < 0.001. Zinc supplementation was used in all cases. Early treatment in ambulatory fever clinics in Saudi Arabia.

9/13 **Positive**

Table. 3: Logistic regression model comparing 28-day clinical outcomes of mild-moderate symptomatic COVID-19 positive patients who received hydroxychloroquine as outpatient compared to supportive care

Clinical outcome	Crude OR (95% CI)	Adjusted OR* (95% CI)	*p-value***
Hospital admission	0.52 (0.44 - 0.63)	0.57 (0.47 - 0.69)	<0.001
ICU admission	0.51 (0.28 - 0.92)	0.63 (0.34 - 1.15)	0.133
Mortality§	0.26 (0.12 - 0.58)	0.36 (0.16 - 0.8)	0.012
ICU admission and/or Mortality	0.45 (0.28 - 0.72)	0.55 (0.34 - 0.91)	0.019

*adjusted for age (reference = age less than 18), male gender, independent comorbidities: (heart disease, chronic lung disease, hypertension, diabetes and other metabolic disorders, chronic kidney disease, malignancy). ICU= intensive care unit.
** for adjusted OR
§ No deaths in ≥ 65 years in the HCQ group.

death, ↓**63.7%**, p=0.01
hospitalization, ↓**38.6%**, p=0.001
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

9/12 **Positive**

Late treatment study

Heberto et al., IJC Heart & Vasculature, doi:10.1016/j.ijcha.2020.100638 (Peer Reviewed)

Implications of myocardial injury in Mexican hospitalized patients with coronavirus disease 2019 (COVID-19)

Observational prospective 254 hospitalized patients, HCQ+AZ mortality odds ratio OR

0.36, p = 0.04.

Ventilation OR 0.20, p = 0.008.

death, ↓**53.6%**, p=0.04
ventilation, ↓**65.6%**, p=0.008
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

9/9 **Positive**

Late treatment study

Alamdari *et al., Tohoku J. Exp. Med., 2020, 252, 73-84, doi:10.1620/tjem.252.73 (Peer Reviewed)*

Mortality Risk Factors among Hospitalized COVID-19 Patients in a Major Referral Center in Iran

Retrospective 459 patients in Iran 93% using HCQ, showing HCQ mortality RR 0.45, p = 0.028. HCQ was the only antiviral that showed a significant difference. Small number of control patients and subject to confounding by indication. Average admission delay 5.72 days.

death, ↓**55.0%**, p=0.03

Source Study Page Submit Corrections or Comments

9/9 **Inconc.**

Early, Late

Kirenga *et al., BMJ Open Respiratory Research, doi:10.1136/bmjresp-2020-000646 (Peer Reviewed)*

Characteristics and outcomes of admitted patients infected with SARS-CoV-2 in Uganda

Prospective 56 patients in Uganda, 29 HCQ and 27 control, showing 25.6% faster recovery with HCQ, 6.4 vs. 8.6 days (p = 0.20). There was no ICU admission, mechanical ventilation, or death.

Treatment delay is not specified but at least a portion of patients appear to have been treated early.

recovery time, ↓**25.6%**, p=0.20, median time to recovery

Source Study Page Submit Corrections or Comments

9/9 **Negative**

Pre-Exposure Prophylaxis study

***Rentsch** et al., medRxiv, doi:10.1101/2020.09.04.20187781 (Preprint)*

Hydroxychloroquine for prevention of COVID-19 mortality: a population-based cohort study

Observational database study of RA/SLE patients in the UK, 194,637 RA/SLE patients with 30,569 having >= 2 HCQ prescriptions in the prior 6 months, HCQ HR 1.03 [0.80-1.33] (HR 0.78 before adjustments).

70 patients with HCQ prescriptions died. One major problem is that there is no knowlege of medication adherence for these 70 - for example, it is possible that they were part of the expected percentage of patients that did not take the medication as prescribed, invalidating the result.

Both confirmed and suspected deaths were included. It is not clear why the authors did not report the result for only confirmed cases. It has been reported that several thousand deaths were incorrectly declared as COVID-19 in the UK.

Other limitations: confounding by use of bDMARDs, confounding by severity of rheumatological disease.

death, **↑3.0%**, p=0.83

Source Study Page Submit Corrections or Comments

9/9 **Inconc.**

Pre-Exposure Prophylaxis study

***Laplana** et al., medRxiv, doi:10.1101/2020.09.03.20158121 (Preprint)*

Lack of protective effect of chloroquine derivatives on COVID-19 disease in a Spanish sample of chronically treated patients

Survey of 319 autoimmune disease patients taking CQ/HCQ with 5.3% COVID-19 incidence, compared to a control group from the general population (matched on age, sex, and region, but not adjusted for autoimmune disease), with 3.4% incidence.

It not clear why authors did not compare with autoimmune patients not on CQ/HCQ. Other research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, Ferri et al. show OR 4.42, $p<0.001$ [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure. If we adjust for the different baseline risk, the result becomes RR 0.36, $p<0.001$, suggesting a substantial benefit for HCQ/CQ treatment (as shown in other studies).

There may also be significant survey bias - those experiencing COVID-19 may be more likely to respond to the survey.

Authors note that they "could not eliminate completely the possibility of some bias due to the intrinsic condition of the individuals within the treatment group that are undergoing chloroquine or derivative drug treatment due to other diseases that alter their health status and may have different comorbidities", however they could account for one significant bias by comparing with matched autoimmune disease patients.

[1] c19study.com/ferri.html

COVID-19 case, ↑**56.0%**, p=0.24

Source Study Page Submit Corrections or Comments

Review

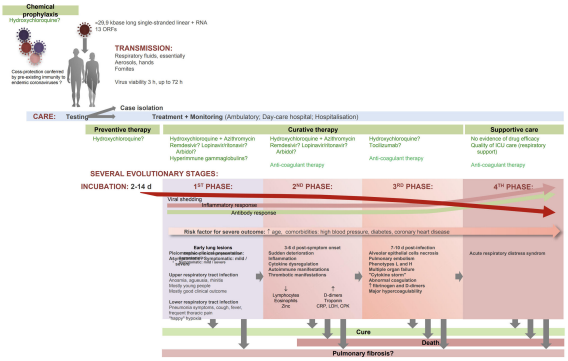
IHU, Expert Review of Clinical Immunology (Review) (Peer Reviewed) (not included in the study count)

Natural history and therapeutic options for COVID-19

Review of the current state of knowledge regarding the natural history of and therapeutic options for COVID-19.

Treatment with an oral combination of hydroxychloroquine, azithromycin and zinc may represent the best current therapeutic option in relation to its antiviral and immunomodulatory effects.

9/7 **Review**



Source Study Page Submit Corrections or Comments

9/5 **Positive**

Late treatment study

Synolaki *et al., medRxiv, doi:10.1101/2020.09.05.20184655 (Preprint)*

Activin/Follistatin-axis deregulation is independently associated with COVID-19 in-hospital mortality

Retrospective 117 patients, 58 HCQ. HCQ, AZ, and other treatments were found to be independently associated with survival when treatment commenced early.

Source Study Page Submit Corrections or Comments

9/4 **Inconc.**

Late treatment study

***Furtado** et al., The Lancet, doi:10.1016/S0140-6736(20)31862-6 (Peer Reviewed)*

Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial

Small RCT comparing the addition of AZ for very late stage patients on ventilation or oxygen. No significant difference was found, OR 1.36, *p*=0.11. One notable result is that even within this extremely late stage population, results suggest increased efficacy with the addition of AZ for patients with earlier use of AZ/HCQ, OR 0.71, *p*=0.28.

Patients received 8g of HCQ over 10 days, approaching the high levels used in the RECOVERY trial (9.2g over 10 days), showing significantly more adverse events than typical trials.

Since all patients were on HCQ, this study does not provide information on the efficacy of HCQ.

Source Study Page Submit Corrections or Comments

9/2 **In Vitro**

In Vitro

***Wang** et al., Phytomedicine, doi:10.1016/j.phymed.2020.153333 (Peer Reviewed) (In Vitro) (not included in the study count)*

Chloroquine and hydroxychloroquine as ACE2 blockers to inhibit viropexis of 2019-nCoV Spike pseudotyped virus

In Vitro study providing novel insights into the molecular mechanism of CQ/HCQ treatment, showing that CQ and HCQ both inhibit the entrance of 2019-nCoV into cells by blocking the binding of the virus with ACE2.

Source Study Page Submit Corrections or Comments

9/2 **Positive**

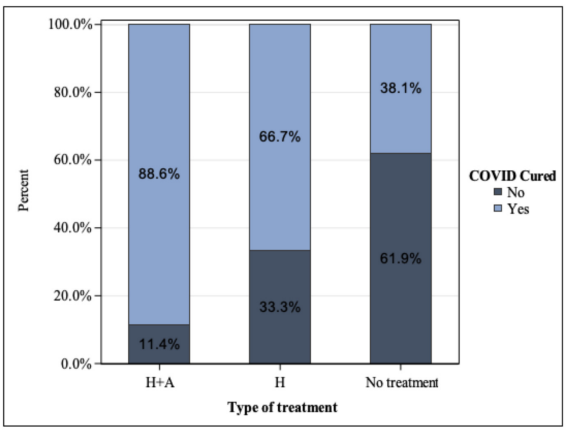
Early treatment study

***Heras** et al., Research Square, doi:10.21203/rs.3.rs-70219/v1 (Preprint)*

COVID-19 mortality risk factors in older people in a long-term care center

Retrospective 100 elderly nursing home patients, HCQ+AZ mortality 11.4% vs. control 61.9%, RR 0.18, p<0.001. Median age 85.

COVID-19 confirmed. 70% treated with HCQ+AZ. Details of differences between groups are not provided, and no adjustments are made. It is not clear how the groups were selected. Authors indicate treatment was early but do not specify the treatment delay.



H+A: Hydroxychloroquine and Azithromycin.
H: Hydroxychloroquine.
No treatment includes Others: Beta-lactam or Quinolone antibiotics.

death, ↓**92.1%**, p<0.001

Source Study Page Submit Corrections or Comments

9/2 **Inconc.**

Pre-Exposure Prophylaxis study

de la Iglesia *et al., medRxiv, doi:10.1101/2020.08.31.20185314 (Preprint)*

Hydroxicloroquine for pre-exposure prophyylaxis for SARS-CoV-2

Analysis of autoimmune disease patients on HCQ, compared to a control group from the general population (matched on age and sex, but not adjusted for autoimmune disease), showing non-significant differences between groups.

Other research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, Ferri et al. show OR 4.42, p<0.001 [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure.

If we adjust for the different baseline risk, the mortality result becomes RR 0.35, p=0.23, suggesting a substantial benefit for HCQ treatment (as shown in other studies).

[1] c19study.com/ferri.html

hospitalization, ↑**50.0%**, p=1.00
COVID-19 case, ↑**42.6%**, p=0.15, suspected COVID-19
COVID-19 case, ↓**7.8%**, p=0.84, confirmed COVID-19

Source Study Page Submit Corrections or Comments

9/1 **Review**

Review

Hecel *et al., Pharmaceuticals, 13:9, 228, doi:10.3390/ph13090228 (Review) (Peer Reviewed) (not included in the study count)*

Zinc(II)—The Overlooked Éminence Grise of Chloroquine's Fight against COVID-19?

Review of zinc as an inhibitor of SARS-CoV-2's RNA-dependent RNA polymerase, and zinc ionophores including CQ/HCQ, showing the latest evidence for zinc and CQ/HCQ having antiviral, and in particular anticoronaviral action.

Source Study Page Submit Corrections or Comments

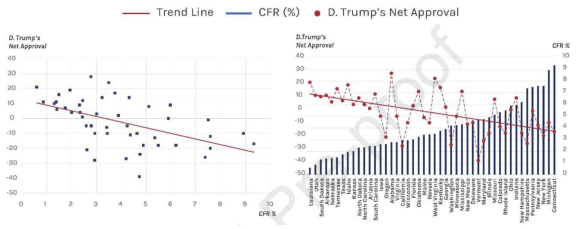
9/1 **Positive**

Early treatment study

Elbazidi *et al., New Microbes and New Infections, doi:10.1016/j.nmni.2020.100749 (Peer Reviewed)*

Pandemic and social changes, political fate

Analysis of US states and countries. Country analysis shows a significant correlation between the dates of decisions to adopt/decline HCQ, and corresponding trend changes in CFR. US state analysis shows a significant correlation between CFR and the level of acceptance of HCQ.



Source Study Page Submit Corrections or Comments

8/29 **Inconc.**

Late treatment study

Castillo et al., Journal of Steroid Biochemistry and Molecular Biology, 203, October 2020, doi:10.1016/j.jsbmb.2020.105751 (Peer Reviewed)

Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study

RCT on calcifediol (25-hydroxyvitamin D) treatment for hospitalized COVID-19 patients showing significantly reduced intensive care unit admissions. All patients received standard care including HCQ+AZ. Significantly lower ICU admission with the addition of Calcifediol - adjusted odds ratio 0.03 [0.003-0.25]. No deaths for Calcifediol (0/50), 2 deaths for SOC (2/26).

	Without Calcifediol Treatment (n = 26)	With Calcifediol Treatment (n = 50)	p value (1d712;2) Fischer Test
Need for ICU			<0.001
Not requiring ICU, n (%)	13 (50)	49 (98)	
Requiring ICU, n (%)	13 (50)	1 (2)	

* Univariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment: 0.02 (95 %CI 0.002–0.17).

** Multivariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment ICU (adjusting by Hypertension and T2DM): 0.03 (95 %CI: 0.003–0.25).

Source Study Page Submit Corrections or Comments

8/28 **Inconc.**

Late treatment study

Fried et al., Clinical Infectious Disease, doi:10.1093/cid/ciaa1268 (Peer Reviewed)

Patient Characteristics and Outcomes of 11,721 Patients with COVID19 Hospitalized Across the United States

Database analysis of 11,721 hospitalized patients, 4,232 on HCQ. Strong evidence for confounding by indication and compassionate use of HCQ. 24.9% of HCQ patients were on mechanical ventilation versus 12.2% control. Ventilation mortality was 70.5% versus 11.6%.

This study does not adjust for the differences in comorbid conditions and disease severity, and therefore does not make a conclusion. Unadjusted HCQ mortality was 24.8% versus control 19.6%. Adjusting for ventilation only gives us 17.7% HCQ versus 19.6% control (adjusting the HCQ group to have the same proportion of ventilation patients), RR 0.90. Hopefully authors can do a full adjustment analysis. Comorbidities may favor control, while patients remaining in the hospital (5.3%) may favor HCQ (other studies show faster resolution for HCQ patients).

death, ↑**27.0%**, p<0.001

Source Study Page Submit Corrections or Comments

8/27 **Positive**

Pre-Exposure Prophylaxis study

Ferri at al., Clinical Rheumatology, doi:0.1007/s10067-020-05334-7 (Peer Reviewed)

COVID-19 and rheumatic autoimmune systemic diseases: report of a large Italian patients series

Analysis of 1641 systemic autoimmune disease patients showing csDMARD (HCQ etc.) RR 0.37, *p*=0.015.

csDMARDs include HCQ, CQ, and several other drugs, so the effect of HCQ/CQ alone could be higher.

This study also confirms that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, OR 4.42, *p*<0.001 (this is the observed real-world risk which takes into account factors such as these patients potentially being more careful to avoid exposure).

(results are for "definite + highly suspected" cases and the main result is presented in the paper as the OR for not taking csDMARDs, we have converted this to RR for taking csDMARDs).

COVID-19 case, **↓63.0%**, p=0.01, risk of COVID-19 case

Source Study Page Submit Corrections or Comments

8/26 **Meta**

Late treatment study

Fiolet et al., Clinical Microbiology and Infection (Peer Reviewed) (meta analysis - not included in study count)

Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a systematic review and meta-analysis

Meta analysis of late stage studies (and one early treatment study with only 2 deaths), showing HCQ RR 0.83 [0.65-1.06], before exclusions RR 0.80 [0.65-1.0].

Authors claim "HCQ alone is not effective", but the result directly contradicts this, RR 0.83 [0.65-1.06], i.e., inconclusive but much more likely to be effective than not.

There are many errors in this meta analysis which introduce critical bias, for example:

- Very biased sample of studies, including <4% of early treatment studies (only 1), and <30% of late treatment studies, focused on negative studies.

- Arshad et al. (propensity matched HR 0.49, *p*=0.009) was excluded because the authors claim a "critical" risk of confounding bias due to steroid use, however steroids were controlled for in the multivariate and propensity analyses [1].

- For Skipper et al., authors use an RR of 1.01, however the study had one hospitalized control death and one non-hospitalized HCQ death. Since the HCQ death was non-hospitalized, it may not be caused by COVID-19, or the patient did not receive standard care, therefore this should not be treated as equal to the control death. Further, medication adherence was only 77%, the HCQ patient may not have taken the medication (Skipper et al. neglects to answer this question). In any case, including a trial with only 1-2 deaths is likely to increase bias.

- Cavalcanti et al. received the lowest bias rating, despite having treatment delayed up to 14 days after symptoms, randomizing 14% of patients in the ICU, having significant protocol deviations, unusually low medication adherence, randomization that resulted in 64.3% male patients (HCQ) vs. 54.2% (control), and excluding patients already receiving longer and potentially therapeutic doses of the study treatments.

- Sbidian el al. received the lowest bias rating, however many more control patients are still in hospital at 28 days suggesting there will be a significant improvement when extending past 28 days.

- The RECOVERY trial received the lowest bias rating, despite using a very high dose likely responsible for the increased mortality. Results of this trial are not relevant to use at normal dosages.

- Inclusion criteria required RT-PCR confirmed cases, but this was disregarded when including Horby et al. (very negative, excessive dose) and Skipper et al.

- Authors do not consider different treatment delays, risk level of patients, differences in dosage, or usage of Zinc.

Also see [2] indicating that this study is fatally flawed. For other problems, see: [3, 4]. This analysis is also missing several recent studies, for a more up-to-date analysis see [5].

[1] ijidonline.com/article/S1201-9712(20)30604-4/fulltext
[2] mediterranee-infection.com/wp-content/uploads/2020/04/Response-to-Fiolet-et...
[3] francesoir.fr/societe-sante/covid-19-les-anti-hydroxychloroquine-et-une-certaine-...
[4] twitter.com/Covid19Crusher/status/1299746474478243841
[5] c19study.com/ihu.html

Source Study Page Submit Corrections or Comments

8/25 **Positive**

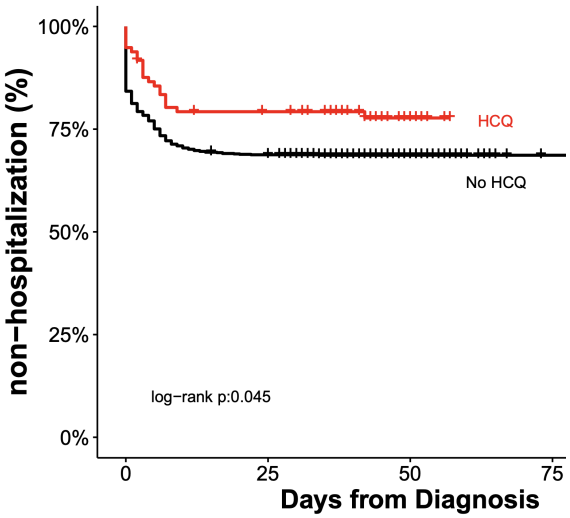
Early treatment study

***Ip** et al., medRxiv, doi:10.1101/2020.08.20.20178772 (Preprint)*

Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: A multi-center observational study

Retrospective 1,274 outpatients, 47% reduction in hospitalization with HCQ with propensity matching, HCQ OR 0.53 [0.29-0.95]. Sensitivity analyses revealed similar associations.

Adverse events were not increased (2% QTc prolongation events, 0% arrhythmias).



hospitalization, ↓**45.9%**, p=0.03
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

8/25 **Positive**

Late treatment study

Di Castelnuovo et al., European J. Internal Medicine, doi:10.1016/j.ejim.2020.08.019 (Peer Reviewed)

Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study

Retrospective 3,451 hospitalized patients, 30% reduction in mortality with HCQ after propensity adjustment, HR 0.70 [0.59 - 0.84].

death, ↓**30.0%**, p<0.0001

Source Study Page Submit Corrections or Comments

8/24 **Positive**

Late treatment study

Catteau et al., Int. J. Antimicrobial Agents, doi:10.1016/j.ijantimicag.2020.106144 (Peer Reviewed)

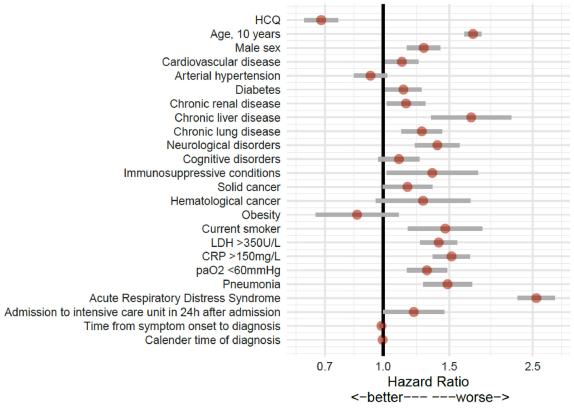
Low-dose Hydroxychloroquine Therapy and Mortality in Hospitalized Patients with COVID-19: A Nationwide Observational Study of 8075 Participants

Retrospective 8,075 hospitalized patients, 4,542 low-dose HCQ, 3,533 control. 35%

lower mortality for HCQ (17.7% vs. 27.1%), adjusted HR 0.68 [0.62–0.76]. Low-dose HCQ monotherapy was independently associated with lower mortality in hospitalized patients.

Patients exposed to others therapies (TCZ, AZ, LPV/RTV) were excluded.

Statistical analysis was performed by an independent group. Calendar time of prescription and immortal time bias was taken into account. Corticosteroids prescriptions was low in both groups.



death, ↓**32.0%**, p<0.0001

Source Study Page Submit Corrections or Comments

8/21 **Positive**

Early treatment study

Ly et al., Preprint, 2020 (Preprint)

Pattern of SARS-CoV-2 infection among dependant elderly residents living in retirement homes in Marseille, France, March-June 2020

Retrospective analysis of retirement homes, HCQ+AZ >= 3 days mortality OR 0.39, *p*=0.026. 1690 elderly residents (mean age 83), 226 infected residents, 116 treated with HCQ+AZ >= 3 days.

Detection via mass screening also showed significant improvements (16.9% vs. 40.6%, OR 0.20, *p*=0.001), suggesting that earlier detection and treatment is more successful.

death, ↓**53.5%**, p=0.03
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

8/21 **Safety**

N/A

Lane et al., The Lancet Rheumatology, doi:10.1016/S2665-9913(20)30276-9 (Peer Reviewed) (not included in the study count)

Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Retrospective study of RA patients using HCQ vs. sulfasalazine (another DMARD). HCQ treatment showed no increased risk in the short term (up to 30 days) among patients with RA. Long term use was associated with excess cardiovascular mortality.

Addition of AZ increased the risk of cardiovascular mortality with combined use up to 30 days. This is several times longer than typical COVID-19 use. This result also comes from just 2 of the 14 databases, with the negative result from just one database (VA) and much lower statistically insignifant difference in mortality from the other database (Clinformatics).

Confounding by indication. Patients conditions vary, the severity of a patient's RA or other conditions was not taken into account. Results varied widely across different databases, and different subsets of databases were used in different analyses. Baseline risk of serious adverse events unknown. Health care database analysis subject to misclassification errors.

Source Study Page Submit Corrections or Comments

8/21 **Positive**

Late treatment study

Gonzalez et al., medRxiv, doi:10.1101/2020.08.18.20172874 (Preprint)

The Prognostic Value of Eosinophil Recovery in COVID-19: A Multicentre, Retrospective Cohort Study on Patients Hospitalised in Spanish Hospitals

Retrospective study focused on eosinophil recovery with 9,644 hospitalized patients in Spain, showing lower mortality for HCQ (14.7% vs 29.2%, $p<0.001$), and AZ (15.3% vs. 18.4%, $p<0.001$). With a multivariate model including potential confounding factors, HCQ and AZ are associated with lower mortality, HCQ OR 0.662, $p=0.057$.

death, **↓26.6%**, p=0.06
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

8/20 **Positive**

Late treatment study

Dubernet et al., J. Global Antimicrobial Resistance, doi:10.1016/j.jgar.2020.08.001 (Peer Reviewed)

A comprehensive strategy for the early treatment of COVID-19 with

azithromycin/hydroxychloroquine and/or corticosteroids: results of a retrospective observational study in the French overseas department of Reunion Island

Retrospective analysis of 36 hospitalized patients showing HCQ/AZ associated with lower ICU admission, *p*=0.008. Median age 66, no mortality. Confounding by indication, however it was patients with hypoxemic pneumonia that were treated with HCQ/AZ, patients were not treated with HCQ/AZ if they didn't need oxygen therapy.

ICU admission, ↓**87.6%**, p=0.008

Source Study Page Submit Corrections or Comments

8/20 **Safety**

Early treatment study

***Prodromos**, C., New Microbes and New Infections, doi:10.1016/j.nmni.2020.100747 (Peer Reviewed) (not included in the study count)*

Hydroxychloroquine is protective to the heart, not harmful: A systematic review

Review concluding that HCQ/AZ does not cause Torsade de Pointes or related deaths, HCQ decreases cardiac events, and HCQ should not be restricted in use for COVID-19 patients because of fear of cardiac mortality.

Source Study Page Submit Corrections or Comments

8/18 **Positive**

Late treatment study

***Pinato** et al., Cancer Discovery, doi:10.1158/2159-8290.CD-20-0773 (Peer Reviewed)*

Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients

Restrospective 890 cancer patients with COVID-19, adjusted mortality HR for HCQ/CQ 0.41, *p*<0.0001.

Confirmed SARS-CoV-2 infection was required, which may help focus on more severe cases. Analysis with Cox proportional hazard model. Potential unmeasured confounders.

death, ↓**59.0%**, p<0.0001

Source Study Page Submit Corrections or Comments

8/15 **Negative**

Late treatment study

***Peters** et al., Clinical Microbiology and Infection, doi:10.1016/j.cmi.2020.10.004 (preprint 8/15) (Peer Reviewed)*

Outcomes of Persons With COVID-19 in Hospitals With and Without Standard Treatment With (Hydroxy)chloroquine

Retrospective study of HCQ use in 9 hospitals in the Netherlands, showing no significant difference in mortality with HCQ/CQ or dexamethasone. Late stage (admitted to hospital with positive test or CT scan abnormalities). 4 of 7 hospitals started treatment only after further deterioration. Short cutoff (21 days) - other studies have shown treated patient cases resolved faster and more control patients remaining in hospital at this time.

In the preprint, 58 of 341 control patients died. In the journal version, 53 of 353 control patients died.

Significant differences between hospitals - HCQ hospitals had significantly older patients with significantly more comorbidities. Non-HCQ hospitals were "tertiary academic centres" whereas HCQ hospitals were "secondary care hospitals". Residual confounding likely. This study compares overcrowded regular hospitals with undercrowded academic hospitals.

A subset of patients were excluded due to transfer to other hospitals. This introduces bias because patients in critical condition are not transferred. For examples, patients benefiting from HCQ treatment may have been transferred to the tertiary centres and excluded from analysis, increasing the percentage of critical cases in the secondary hospitals.

Among the seven (H)CQ-hospitals, the timing of start of (H)CQ treatment differed; three hospitals started at the moment of COVID-19 diagnosis, four started after diagnosis but only when patients clinically deteriorated e.g., when there was an increase in respiratory rate or increase in use of supplemental oxygen.

Most patients received CQ instead of the safer HCQ, receiving late treatment with CQ. Patients were given an initial dose of 600mg CQ then every 12 hours, for 5 days a dose of 300 mg, for a total of 3600mg CQ. This dose is likely to be toxic, see for example [1].

Authors mention a subset of hospitals started treatment relatively earlier, which seems like the most important area to analyze, but no results are provided.

[1] apps.who.int/iris/bitstream/handle/10665/65773/WHO_MAL_79.906.pdf

death, ↑**9.0%**, p=0.57

Source Study Page Submit Corrections or Comments

8/14 **Inconc.**

Late treatment study

Abd-Elsalam *et al., American Journal of Tropical Medicine and Hygiene, 10.4269/ajtmh.20-0873 (Peer Reviewed)*

Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study

Small RCT in Egypt with 97/97 HCQ/control patients, showing 58% more recovery @28days for HCQ (53.6% HCQ, 34% control), *p*=0.009 (0.06 in the paper refers to the 5 combined recovery/death/ICU values).

No significant difference in ventilation and mortality (<=6 examples in each case). Authors note the "sample size was not adequately powered for [the] survival endpoint".

Other studies have also shown treated patient cases resolved faster. Continuing analysis past 28 days would be useful. Group characteristics are given, with for example 36% vs. 26% smokers, but they do not identify which group is which. Group 1 and 2 have 97 patients but the total given is 175.

death, ↑**20.0%**, p=1.00
no recovery, ↓**30.0%**, p=0.009, risk of no recovery at day 28

Source Study Page Submit Corrections or Comments

8/13 **Negative**

Late treatment study

Roomi *et al., J. Medical Internet Research, doi:10.2196/21758 (Peer Reviewed)*

Efficacy of hydroxychloroquine and tocilizumab in patients with COVID-19: A single-center retrospective chart review

Retrospective 176 hospitalized patients (144 HCQ, 32 control) showing no significant differences with HCQ or TCZ. Confounding by indication.

death, ↑**37.7%**, p=0.54
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

8/11 **Safety**

Early treatment study

Bakhshaliyev *et al., J. Electrocardiology, doi:10.1016/j.jelectrocard.2020.08.008 (Peer Reviewed) (not included in the study count)*

The effect of 5-day course of hydroxychloroquine and azithromycin combination on QT interval in non-ICU COVID19(+) patient

Safety study of 109 patients showing 5 days of HCQ+AZ did not lead to clinically significant QT prolongation or other conduction delays compared to baseline ECG in non-ICU patients.

Source Study Page Submit Corrections or Comments

8/11 **Negative**

Late treatment study

Saleemi *et al., medRxiv, doi:10.1101/2020.08.05.20151027 (Preprint)*

Time to negative PCR from symptom onset in COVID-19 patients on Hydroxych loroquine and Azithromycin - A real world experience

Retrospective 65 HCQ+AZ, 20 control patients, showing median time to negative PCR of 23 days for HCQ+AZ vs. 19 days for control. Confounding by indication. 100% of non-HCQ group had mild disease vs. 63% of the HCQ+AZ group. More comorbidities and symptoms in the HCQ+AZ group.

time to viral-, ↑**21.0%**, p<0.05, median time to PCR-

Source Study Page Submit Corrections or Comments

8/8 **Inconc.**

Late treatment study

Lopez *et al., Int. J. Antimicrob. Agents, doi:/j.ijantimicag.2020.106136 (Peer Reviewed)*

Effects of Hydroxychloroquine on Covid-19 in Intensive Care Unit Patients: Preliminary Results

Small retrospective study of 29 ICU patients comparing those with HCQ plasma concentration within target to those with a concentration below the target value, with no significant differences found. Mortality in the on-target group was 0% versus 17% for the off-target group, mortality relative risk 0.14, p = 0.16.

Source Study Page Submit Corrections or Comments

8/6 **Review**

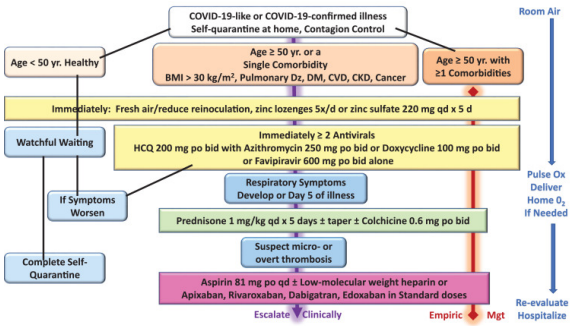
Review

McCullough *et al., The American Journal of Medicine, doi:10.1016/j.amjmed.2020.07.003 (Review) (Peer Reviewed) (not included in the study count)*

Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection

Review of pathophysiological principles related to early outpatient treatment and therapeutic approaches including reduction of reinoculation, combination antiviral therapy, immunomodulation, antiplatelet/antithrombotic therapy, and administration of oxygen, monitoring, and telemedicine.

Proposes an algorithm based on age and comorbidities that allows for a large proportion to be monitored and treated at home during self-isolation with the aim of reducing the risks of hospitalization and death.



Source Study Page Submit Corrections or Comments

8/6 **Meta**

PEP, Early, Late

Watanabe *et al., Open Letter (Letter) (meta analysis - not included in study count)*

Concerns regarding the misinterpretation of statistical hypothesis testing in clinical trials for COVID-19

Open letter signed by 38 professors and doctors regarding misinterpretation of statistics in HCQ RCTs.

Authors note [1] that data from RCTs for early treatment in outpatients to date actually show favorable effects, especially in high-risk patients such as the elderly, where efficacy was up to three times higher than in young people. Because most samples were made up of young people without comorbidities, the studies were statistically inconclusive with the entire samples. Authors note that instead of the papers reporting this, they incorrectly claim that the treatment had no effect compared to the placebo. “This misinterpretation in statistical tests is well known and explained in most undergraduate books in the field,” says Watanabe. "An article published in Nature last year states that about 51% of the work on clinical trials with this type of result has incorrect conclusions."

[1] veja.abril.com.br/saude/especialistas-contestam-estudos-que-nao-viram-benefic...

Source Study Page Submit Corrections or Comments

8/5 **Negative**

Pre-Exposure Prophylaxis study

Singer *et al., Annals of the Rheumatic Diseases, doi:10.1136/annrheumdis-2020-218500 (Letter)*

Hydroxychloroquine ineffective for COVID-19 prophylaxis in lupus and rheumatoid arthritis

Comparison of the percentage of SLE/RA patients on immunosuppressants that were taking HCQ, for COVID-19 diagnosis versus other infections or outpatient visits, finding a similar percentage in each case.

No mortality of severity information is provided to determine if HCQ treated patients fared better. No adjustment for concomitant medications or severity.

COVID-19 case, ↑**9.0%**, p=0.62

Source Study Page Submit Corrections or Comments

8/4 **Inconc.**

Late treatment study

***Kamran** et al., medRxiv, doi:10.1101/2020.07.30.20165365 (Preprint)*

Clearing the fog: Is HCQ effective in reducing COVID-19 progression: A randomized controlled trial

Study of 349 low-risk hospitalized patients with 151 non-consenting or ineligible patients used as controls. SOC included zinc, vitamin C and vitamin D. A statistically significant improvement in PCR negativity is shown at day 7 with HCQ treatment, 52.1% (HCQ) versus 35.7% (control), *p*=0.001, but no statistically significant difference at day 14, or in progression. Patients were relatively young and there was no mortality. Only 3% of patients had any disease progression and all patients recovered, so there is little if any room for treatment benefit. Progression among higher-risk patients with comorbidities was lower with treatment (12.9% versus 28.6%, *p*=0.3, very few cases).

Despite the title, this is not an RCT since patients self-selected the arm, or were chosen based on allergies/contraindications. The treatment group had about twice the number of patients with comorbidities. Treatment delay is unknown - it was recorded but not reported in the paper.

Viral load was not measured. As with other studies, PCR may detect non-replicable viral nucleic acid, this is more likely at day 14. Details on the test accuracy are not provided, authors note that RT-PCR sensitivity ranges from 34-80%.

disease progression, ↓**5.0%**, p=1.00
no virological cure, ↑**10.0%**, p=0.52, risk of viral+ at day 14
no virological cure, ↓**25.5%**, p=0.001, risk of viral+ at day 7

Source Study Page Submit Corrections or Comments

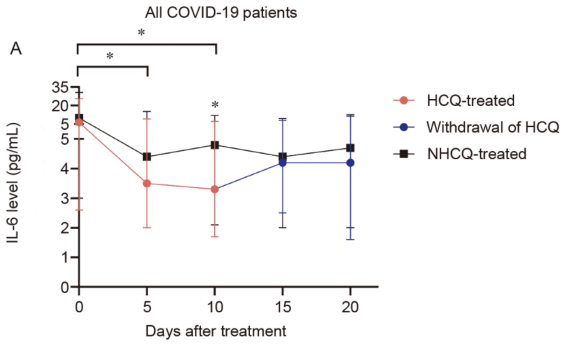
8/3 **Positive**

Late treatment study

***Yu** et al., Science China Life Sciences, 2020 Aug 3, doi:10.1007/s11427-020-1782-1 (Letter)*

Beneficial effects exerted by hydroxychloroquine in treating COVID-19 patients via protecting multiple organs

Retrospective 2,882 patients in China, median age 62, 278 receiving HCQ, median 10 days post hospitalization, showing that HCQ treatment can reduce systemic inflammation and inhibit the cytokine storm, thus protecting multiple organs from inflammatory injuries, such as detoxification in the liver and attenuation of cardiac injury. IL-6 levels significantly reduced after HCQ treatment, $p<0.05$, and elevated after HCQ withdrawal. The significantly lower dose used here is potentially related to the different observations from the RECOVERY trial results. Authors suggest that treatment should be started as soon as possible.



Source Study Page Submit Corrections or Comments

Late treatment study

Davido et al., Int. J. Antimicrobial Agents, 2020, doi:10.1016/j.ijantimicag.2020.106129 (Peer Reviewed)

8/2 **Positive**

Impact of medical care including anti-infective agents use on the prognosis of COVID-19 hospitalized patients over time

Retrospective of 132 hospitalized patients. HCQ+AZ(52)/AZ(28) significantly reduced death/ICU, HR=0.45, $p=0.04$. Adjusted for Charlson Comorbidity Index (including age), obesity, O2, lymphocyte count, and treatments. Mean delay from admission to treatment 0.7 days.

combined intubation/hospitalization, ↓**55.0%**, p=0.04

Source Study Page Submit Corrections or Comments

8/2 **In Vitro**

In Vitro

Sheaff, R., bioRxiv, doi:10.1101/2020.08.02.232892 (Preprint) (In Vitro) (not included in the study count)

A New Model of SARS-CoV-2 Infection Based on (Hydroxy)Chloroquine Activity

In vitro study presenting a new theory on SARS-CoV-2 infection and why HCQ/CQ provides benefits, which potentially explains the observed relationships with smoking, diabetes, obesity, age, and treatment delay, and confirms the importance of accurate dosing. Metabolic analysis revealed HCQ/CQ inhibit oxidative phosphorylation in mitochondria (likely by sequestering protons needed to drive ATP synthase), inhibiting infection and/or slowing replication.

Source Study Page Submit Corrections or Comments

7/29 **Positive**

Late treatment study

***D'Arminio Monforte** et al., Int. J. Infectious Diseases, doi:10.1016/j.ijid.2020.07.056 (Letter)*

Effectiveness of Hydroxychloroquine in COVID-19 disease: A done and dusted situation?

HCQ+AZ adjusted death HR 0.44, *p*=0.009. Propensity scores include baseline COVID-19 disease severity, age, gender, number of comorbidities, cardio-vascular disease, duration of symptoms, date of admission, baseline plasma CRP. IPW censoring. Retrospective study of 539 COVID-19 hospitalized patients in Milan, with treatment a median of 1 day after admission. HCQ 197 patients, HCQ+AZ 94, control 92. Control group received various other treatments. Authors excluded people receiving other drugs which could have biased the effect of HCQ when used in combination. Residual confounding is possible (e.g., people with CVD were more frequent in control), however people in the control group were more likely to require mechanical ventilation.

death, **↓34.0%**, p=0.12
death, **↓56.0%**, p=0.009, HCQ+AZ

Source Study Page Submit Corrections or Comments

7/28 **Inconc.**

Late treatment study

***BaŞaran** et al., Turk. J. Med. Sci., doi:10.3906/sag-2006-173 (Peer Reviewed)*

Outcome of Non-Critical COVID-19 Patients with Early Hospitalization and Early Antiviral Treatment Outside the ICU

Observational study of 174 hospitalized patients in Turkey, median age 45.4, 23 treated with HCQ, 113 with HCQ+AZ, and 32 with regimens including favipiravir. 75% reduction in the median time to clinical improvement for HCQ+AZ vs. FAV, RR 0.25, *p*<0.001. 83% reduction for HCQ. However, there was significant confounding by indication.

There were no significant adverse events.

Source Study Page Submit Corrections or Comments

7/26 **Inconc.**

Post Exposure Prophylaxis study

***Mitjà** et al., medRxiv, doi:10.1101/2020.07.20.20157651 (Preprint)*

A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and Disease

Death rate reduced from 0.6% to 0.4%, RR 0.68, not statistically significant due to low incidence (8 control cases, 5 treatment cases).

For positive symptomatic cases, a greater effect is seen for nursing home residents, RR=0.49 [0.21 - 1.17], vs. overall 0.89, possibly because the exposure events are identified faster in this context, versus home exposure where testing of the source may be more delayed. The trial is too small for significance here. If the trend continued this result would be significant at $p<0.05$ after about 25% more patients were added.

There are 2 groups in this study: PCR+ at baseline (n=314) and PCR- at baseline (n=2000), which should be separated as they are different populations (primary outcome rates 18.6% and 22.2% compared to 3.0% and 4.3%). PCR+ already have COVID-19, so PEP analysis should be for the 2,000 PCR-, showing symptomatic COVID-19 of 4.3% (control) and 3.0% (treatment), RR 0.7, $p=0.154$.

The paper has different RR values here, stating that they are adjusted for contact-level variables. It is not clear how they are computed - the adjusted RR for the overall sample is 4% lower, for PCR+ it is 20% lower, but for PCR- it is 107% higher, even though PCR- represents 86% of the sample.

Hopefully, supplementary data will provide a breakdown on cases in this PCR-@baseline sample by number of days since exposure, and also provide relevant hospitalisation and death results.

Enrollment was up to 7 days after exposure, median 4 days. Treatment delay is unclear. The exposure event timing is not detailed. It appears to be based on the date of a positive test for a contact, which is likely to be much later than the actual exposure time. 13.1% were already positive at baseline, which is consistent with the actual exposure time being significantly earlier. PCR testing has a very high false-negative rate in early stages (e.g., 100% on day 1, 67% on day 4, and 20% on day 8 [1]), hence it is likely that a much higher percentage were infected at an unknown time before enrollment. Medication administration is not detailed. Sensitivity and specificity of the tests is not provided.

Given the delay identifying index cases, PCR test delay, and PCR false negative rate at early stages, the treatment delay in general was very long and could be over 2 weeks.

The RR for non-PCR positive at baseline is 0.74. Including the PCR-positive at baseline patients reduced this to 0.89. This is also consistent with earlier treatment being more effective.

The paper does not mention zinc. Zinc deficiency in Spain has been reported at 83% [2], this may significantly reduce effectiveness. HCQ is a zinc ionophore which increases cellular uptake, facilitating significant intracellular concentrations of zinc, and zinc is known to inhibit SARS-CoV RNA-dependent RNA polymerase activity, and is widely thought to be important for effectiveness with SARS-CoV-2 [3].

This study focuses on the existence of symptoms or PCR-positive results, however severity of symptoms is more important. Research has shown HCQ concentrations can be much higher in the lung compared to plasma [4], which may help minimize the occurrence of severe cases and death.

There is a treatment-delay response relationship consistent with an effective treatment, however the authors only provide 3 ranges and do not break down the earliest treatment delay times.

The definition of COVID-19 symptoms is very broad - just existence of a headache alone or muscle pain alone was considered COVID-19. There was an overall very low incidence of confirmed COVID-19 (138 cases across both arms). There were no serious adverse events that were adjudicated as being treatment related. Authors exclude those with symptoms in the previous two weeks, however, those with symptoms up to several months before may still test PCR-positive even though there may be no viable virus.

There appears to be incorrect data. Table 2, secondary outcomes, control, hospital/vital records shows that 8 of 1042 is 9.7% (we get 0.8%).

Nasopharyngeal viral load analysis issues include test unreliability and temporo-spatial differences in viral shedding [5].

In summary, this study appears positive in the context of very delayed treatment and very small sample sizes, however we have classified it as inconclusive for now pending further analysis and feedback. Preliminary analysis. Supplementary Appendix is not currently available. Please submit any corrections or comments.

[1] acpjournals.org/doi/10.7326/M20-1495
[2] mdpi.com/2072-6643/9/7/697
[3] infezmed.it/index.php/article?Anno=2020&numero=2&ArticoloDaVisualizzare=Vo...
[4] ncbi.nlm.nih.gov/pmc/articles/PMC7122276/
[5] journal.chestnet.org/article/S0012-3692(20)31718-9/fulltext

death, ↓**32.0%**, p=0.58
COVID-19 case, ↓**30.0%**, p=0.15, baseline pcr- risk of cases

Source Study Page Submit Corrections or Comments

7/24 **Positive**

Pre-Exposure Prophylaxis study

Khurana et al., medRxiv, doi:10.1101/2020.07.21.20159301 (Preprint)

Prevalence and clinical correlates of COVID-19 outbreak among healthcare workers in a tertiary level hospital

Study of hospital health care workers showing HCQ prophylaxis reduces COVID-19 significantly, OR 0.30, *p*=0.02. 94 positive health care workers with a matched sample of 87 testing negative. Full course prophylaxis was important in this study which used a low dose of 400mg/week HCQ (800mg for week 1), so it may take longer to reach therapeutic levels. Actual benefit of HCQ may be larger because severity of symptoms are not considered here but HCQ may also reduce severity.

COVID-19 case, ↓**51.0%**, p=0.02
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

7/23 **Negative**

Late treatment study

Cavalcanti et al., NEJM, July 23, 2020, doi:10.1056/NEJMoa201901 (Peer Reviewed)

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19

Late stage RCT of 667 hospitalized patients with up to 14 days of symptoms at enrollment and receiving up to 4 liters per minute supplemental oxygen, not finding a significant effect after 15 days.

Authors note: "the trial cannot definitively rule out either a substantial benefit of the trial drugs or a substantial harm", sample sizes are too small.

The paper uses the terms mild and moderate, however all patients had serious enough disease to be hospitalized, and 14% were actually randomized in the ICU.

The trial had significant protocol deviations and unusually low medication adherence. Randomization resulted in 64.3% male patients (HCQ) vs. 54.2% (control) which may significantly affect results due to the much higher risk for male patients.

Authors note: "our aim was to exclude patients already receiving longer and potentially therapeutic doses of the study treatments" in explanation for why the study protocol was changed to exclude patients with previous use of the medications >24hrs. Analyzing these patients rather than excluding them may have revealed effectiveness with early use as shown in other studies.

The trial initially required enrollment within 48 hours of admission and was changed to remove this requirement, this change is likely to reduce effectiveness because enrollment was moved later, compared to the time the disease became serious enough for hospitalization. Total HCQ dosage 5.6g.

A correction for 17 errors has been published: [1]

[1] nejm.org/doi/full/10.1056/NEJMx200021

death, ↓16.0%, p=0.77, HCQ+HCQ/AZ risk of death
hospitalization, ↑28.0%, p=0.30, HCQ+HCQ/AZ risk of hospitalization

Source Study Page Submit Corrections or Comments

7/22 **In Vitro**

In Vitro

Hoffmann *et al., Nature, (2020), doi:10.1038/s41586-020-2575-3 (Peer Reviewed) (In Vitro) (not included in the study count)*

Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2

The title of this paper does not appear to match the results. Fig. 1b @100uM shows C Q results in a ~4.5 fold decrease (on a linear scale) in extracellular virus, *p*=0.05, after 24 hours (we do not see the supplementary data at this time so this is estimated from the graph). This decrease may continue if examined over longer time periods. Fig. 1a shows a ~45-50% entry inhibition @100uM for HCQ/CQ (*p*=0.0005/0.0045), ~10-30% @10uM (*p*=0.13/0.99). Inhibition is significantly better with Vero cells. Note that the safe concentration in practice for different cells is not well known, Keyaerts et al. find CC50 of 261uM [1].

In vitro study of CQ and HCQ inhibition of SARS-CoV-2 into Vero (kidney), Vero-TMPRSS2, and Calu-3 (derived from human lung carcinoma) cells.

Authors reportedly used sodium pyruvate which may inhibit CQ from entering cells [2].

Although there are several theories on how HCQ may help with COVID-19, authors do not consider the most common theory where HCQ functions as a zinc ionophore, facilitating significant intracellular concentrations of zinc. Zinc is known to inhibit SARS-CoV RNA-dependent RNA polymerase activity, and is widely thought to be important for effectiveness with SARS-CoV-2 [3].

Calu-3 is one of many cell lines derived from human lung carcinomas [4]. Calu-3 cells resemble serous gland cells. They do not express 15-lipoxygenase, an enzyme specifically localized to the surface epithelium, but they do express secretory component, secretory leukocyte protease inhibitor, lysozyme, and lactoferrin, all markers of serous gland cells. [5] note that the absence of systemic inflammation, circulatory factors, and other paracrine systemic influences is a potential limitation of the isolated cell system.

RT-PCR is used, we note that nucleic acid may persist even after the virus is no longer viable [6].

It is unclear how the authors conclude "CQ does not block SARS-CoV-2 infection of Calu-3" cells, when the results show statistically significant inhibition at higher concentrations.

Further, it is unclear how the authors go from these results in one specific type of pulmonary adenocarcinoma cells that resemble serous gland cells, *in vitro*, into the title of the paper which claims no inhibition in lung cells.

Further, it is unclear how another leap is made to "will not be effective against COVID-19" given the multiple theories of HCQ/CQ effectiveness.

[1] c19study.com/keyaerts.html
[2] twitter.com/JaclynHord/status/1302680394244947969
[3] infezmed.it/index.php/article?Anno=2020&numero=2&ArticoloDaVisualizzare=Vo...
[4] journals.physiology.org/doi/pdf/10.1152/ajplung.1994.266.5.L493
[5] journals.physiology.org/doi/pdf/10.1152/ajplung.1994.266.5.L493
[6] fda.gov/media/136472/download

Source Study Page Submit Corrections or Comments

7/22 **Negative**

Late treatment study

***Rivera** et al., Cancer Discovery, doi:10.1158/2159-8290.CD-20-0941 (Peer Reviewed)*

Utilization of COVID-19 Treatments and Clinical Outcomes among Patients with Cancer: A COVID-19 and Cancer Consortium (CCC19) Cohort Study

Retrospective cancer patients, showing adjusted OR 1.03 [0.62-1.73] for HCQ. The study reports the number of HCQ+AZ patients but they do not provide results for HC Q+AZ (only HCQ + any other treatment). Significant confounding by indication and compassionate use is likely.

death, ↑**2.4%**, p=0.90
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

7/22 **Negative**

Late treatment study

***Kelly** et al., British Journal of Clinical Pharmacology, doi:10.1111/bcp.14482 (Peer Reviewed)*

Clinical outcomes and adverse events in patients hospitalised with COVID-19, treated with off-label hydroxychloroquine and azithromycin

Retrospective 82 hospitalized patients HCQ/AZ, 52 SOC, not finding statistically significant differences. Confounding by indication - authors note that the HCQ/AZ patients were more severely ill, and do not attempt to adjust for confounders.

death, ↑**143.0%**, p=0.03

Source Study Page Submit Corrections or Comments

7/21 **Positive**

Late treatment study

Bernaola et al., medRxiv, doi:10.1101/2020.07.17.20155960 (Preprint)

Observational Study of the Efficiency of Treatments in Patients Hospitalized with Covid-19 in Madrid

HCQ HR 0.83 [0.77-0.89] based on propensity score matched retrospective analysis of 1,645 hospitalized patients. Prednisone HR 0.85 [0.82-0.88], 14 other medications showed either no signicant benefit or a negative effect.

death, ↓**17.0%**, p<0.0001

Source Study Page Submit Corrections or Comments

7/20 **Meta**

Early treatment study

***Risch**, H., American Journal of Epidemiology, July 20, 2020, doi:10.1093/aje/kwaa152 (Peer Reviewed) (meta analysis - not included in study count)*

Response to: “Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients” and “Re: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis”

Updated meta analysis including 7 new studies of high-risk outpatients, for a total of 12 studies, all showing significant benefit.

Table 1. Studies Examining High-Risk Outpatient COVID-19 Disease Treated Early with HCQ

Principal Investigator	Location	Subject Status	Number Treated with HCQ	Number of Comparison Subjects	Other Medications with HCQ	Comparison-Subject Medications	Outcome	Direction of Benefit	RR (95% CI), Statistical Significance or Number of Deaths	Reference
P. Gautret	Marseille, France	Mixed older adults	6	14	AZ	HCQ alone	Nasopharyngeal viral clearance	Reduced risk	7.4 (1.12-48.4)	(6)
V. Zelenko	Kiryas Joel, NY	High-risk	405 (series 1)		AZ, zinc sulfate		Mortality	Reduced risk	2 deaths/405	(16)
V. Zelenko	Kiryas Joel, NY	High-risk	400 (series 2)		AZ, zinc sulfate		Mortality	Reduced risk	0 deaths/400	PC[a]
R. Barbosa Esper	São Paulo, Brazil	Mixed older adults	412	224	AZ	SOC	Hospitalization	Reduced risk	0.35 (0.14-0.87)	(17)
I. Ahmad	Long Island, NY Nursing Home	High-risk	200		Dox		Mortality	Reduced risk	9 deaths/200	(18), PC[b]
J.-C. Lagier	Marseille, France	High-risk	199	199	AZ	Propensity-score matched; HCQ or AZ alone or neither	Mortality	Reduced risk	0.41 (0.17-0.99)	(19)
M. Leriger	Indiana Nursing Homes	High-risk	105	113	None, AZ, Dox	SOC, +AZ or Dox	Mortality	Reduced risk	*P*<.05	PC[c]
L. Kacmar	Aurora, IL	High-risk	68		AZ		Mortality	Reduced risk	0 deaths/68	PC[d]
S. Fonseca	Brazil HMO	High-risk	159	558	Prednisone	Neither HCQ nor Prednisone	Hospitalization	Reduced risk	*P*<.05	PC[e]
B. Procter	McKinney, TX	High-risk	50		AZ, zinc sulfate, losartan, aspirin		Mortality	Reduced risk	0 deaths/50	PC[f]
S. Crawford	Festus, MO Nursing Home	High-risk	52		Rehydration		Mortality	Reduced risk	0 deaths/52	(20)
B. Tyson	El Centro, CA	High-risk	219		AZ (2 with Dox)		Mortality	Reduced risk	0 deaths/219	PC[g]

Source Study Page Submit Corrections or Comments

7/18 **Meta**

Post Exposure Prophylaxis study

Watanabe, M., arXiv.org, arXiv:2007.09477 (Preprint) (meta analysis - not included in study count)

Efficacy of Hydroxychloroquine as Prophylaxis for Covid-19

Secondary analysis of Boulware et al.'s PEP trial and treatment delay-response data, confirming that HCQ is effective when used early, $p<0.01$.

The effectiveness found is especially notable considering the limitations of the study. Treatment was relatively late, with enrollment up to
4 days after exposure, and an unspecified shipping delay. While the paper does not provide shipping details, the study protocol gives some detail allowing us to estimate the treatment delay as ~70 to 140 hours after exposure on average for the 1-4 days since enrollment specified in the paper (we will update this when authors respond to our request for details). There was only 75% medication adherence, including 16% who did not take the medication at all. The study relies on Internet surveys.

Some issues have been raised with this analysis. 1-tailed vs. 2-tailed tests - this is debatable, an argument can be made for both cases. However, it doesn't affect the conclusion in terms of the delay-response relationship showing statistically significant efficacy. Secondly, the paper projects the "1-4" day results to a day "0" result (in reality about 46 hours later in all cases), while the trend may well continue, we do not know this. However it doesn't change the outcome that the 1-4 day results show a statistically significant delay-response relationship.

Source Study Page Submit Corrections or Comments

Late treatment study

McGrail et al., medRxiv, doi:10.1101/2020.07.17.20156521 (Preprint)

COVID-19 Case Series at UnityPoint Health St. Luke's Hospital in Cedar Rapids, IA

7/19 **Inconc.**

HCQ+AZ early in the epidemic had a fairly good success rate with few complications, 86% of HCQ patients survived and 92% of HCQ+AZ patients. Patients not receiving either had 93% survival but were not considered comparable because the treated groups were significantly more ill (100% hypoxic at admission vs. 59%) and this study does not adjust for the differences.

Transition from an early intubation strategy to aggressive utilization of high flow nasal cannula and noninvasive ventilation (i.e, BiPAP) was successful in freeing up ICU resources.

death, ↑**70.0%**, p=0.69

Source Study Page Submit Corrections or Comments

7/17 **Inconc.**

Late treatment study

Lyngbakken *et al., Research Square, doi:10.21203/rs.3.rs-44055/v1 (Peer Reviewed)*

A pragmatic randomized controlled trial reports lack of efficacy of hydroxych loroquine on coronavirus disease 2019 viral kinetics

Small RCT of nasopharyngeal viral load not showing significant differences. The rate of reduction for HCQ was 0.24 [0.03-0.46] RNA copies/mL/24h, and 0.14 [-0.10-0.37] for the control group (71% faster with HCQ but not statistically significant with the small sample size of 27 HCQ and 26 control patients). Analysis only over 96 hours.

NCT04316377

death, ↓**3.7%**, p=1.00
time to viral-, ↓**71.0%**, p=0.51, improvement in viral load reduction rate

Source Study Page Submit Corrections or Comments

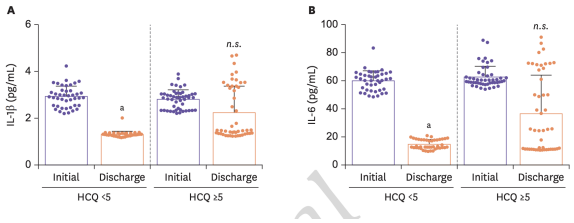
Early treatment study

Hong *et al., Infect. Chemother., 2020, doi:10.3947/ic.2020.52.e43 (Peer Reviewed)*

Early Hydroxychloroquine Administration for Rapid Severe Acute Respiratory Syndrome Coronavirus 2 Eradication

HCQ 1-4 days from diagnosis was the only protective factor against prolonged viral shedding found, OR 0.111, *p*=0.001. 57.1% viral clearance with 1-4 days delay vs. 22.9% for 5+ days delayed treatment. Authors report that early administration of HCQ significantly ameliorates inflammatory cytokine secretion and that COVID-19 patients should be administrated HCQ as soon as possible. 42 patients with HCQ 1-4 days from diagnosis, 48 with HCQ 5+ days from diagnosis.

7/16 **Positive**



no virological cure, ↓**64.9%**, p=0.001, risk of prolonged viral shedding
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

7/16 **Inconc.**

Early treatment study

Skipper et al., Annals of Internal Medicine, doi:10.7326/M20-4207 (Peer Reviewed)

Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial

~70 to 140 hour (inc. shipping) delayed outpatient treatment with HCQ reduced combined hospitalization/death by 50%, *p*=0.29 (5 HCQ cases, 10 control cases), and reduced hospitalization by 60%, *p*=0.17. There was one hospitalized control death and one non-hospitalized HCQ death. It is unclear why there was a non-hospitalized death, external factors such as lack of standard care may be involved. Excluding that case results in one control death and zero HCQ deaths (not statistically significant but noted as reducing mortality is the most important outcome). Details for the hospitalizations and deaths such as medication adherence and treatment delay may be informative but are not provided.

The paper states the end point was changed from hospitalization/death to symptom severity because they would have required 6,000 participants. However, if the observed trend continued, they would hit 95% significance on the reduction in hospitalization at ~725 patients, and 95% on the reduction in combined hospitalization/death at ~1,145 patients, which is a lot less than 6,000, and also less than the original plan of 1,242 patients. We hope the trial can be continued for statistical significance.

Treatment is relatively late, ~70 to 140 hours after symptoms, including the shipping delay. The paper does not mention the shipping delay but partial details are provided in the study protocol. They are not clear but indicate no shipping on the weekends and a possible 12pm cutoff for same day dispensing and mailing. Assuming that enrollments were evenly distributed between 6am and 12am each day, we get an average of ~46 hours shipping delay. We have asked for shipping details and will update with more accurate values when available. In any case the treatment delay is quite long and there is no overlap with the more typical delays used such as 0 - 36 hours for oseltamivir.

The paper compares 0 - 36 hour delayed treatment with oseltamivir (influenza) and ~70 to 140 hour delayed treatment with HCQ (COVID-19), noting that oseltamivir seemed more effective. However, a more comparable study is McLean (2015) who showed that 48 - 119 hour delayed treatment with oseltamivir has no effect. This suggests that HCQ is more effective than oseltamivir, and that HCQ may still have significant effect for some amount of delay beyond the delay where oseltamivir is effective.

6 people were included that enrolled with >4d symptoms, although they do not match the study inclusion criteria. This reduces observed effectiveness. The paper says 56% (236) were enrolled within 1 day of symptoms, but results show only 40% for "<1d", 56% is possibly for <48hrs, we have asked for clarification.

Patients in this study are relatively young and most of them recover without assistance. This reduces the room for a treatment to make improvements. The maximum improvement of an effective treatment would be expected before all patients approach recovery, as shown in the figure below. Authors focus on the end result where most have recovered, but it is more informative to examine the curve and the point of maximum effectiveness. Authors did not collect data for every day

but they do have interim results for days 3, 5, 10. The results are consistent with an effective treatment and show a statistically significant improvement, p = 0.05, at day 10 (other unreported days might show increased effectiveness).

Results also show a larger treatment effect for those >50, not statistically significant due to the small sample, but noted as COVID-19 risk dramatically increases with age. The effect may be more visible here because younger patients may on average have more mild cases with less room for improvement. In general patients in this study have relatively mild symptoms on average, limiting the chance to observe improvement.

The study relies on Internet surveys. Known fake surveys were submitted to the similar PEP trial and there could be an unknown number of undetected fake surveys in both trials. The study shows a high incidence of side effects in the placebo arm, which could be in part due to fake entries [1].

The granularity change in the histograms of Figure S4 raise concerns [2]. Data on increasing severity, less affected by the lower bound where everyone has recovered, also supports effectiveness [3].

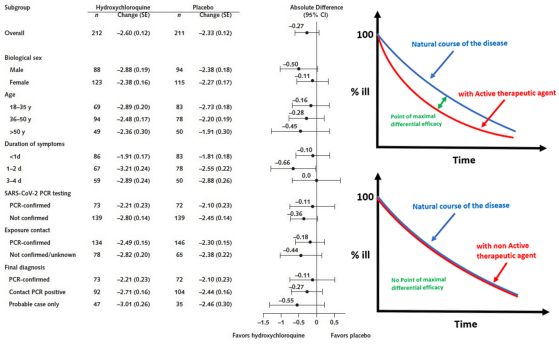
Research shows the placebo used in the US may be protective for COVID-19 [4] so the true effectiveness of HCQ could be higher than observed.

Treatment delay reporting has changed from the companion PEP trial which reported results for enrollment delays 1, 2, 3, and 4 separately (and from which we can confirm a statistically significant delay-response relationship), while this trial combines 1-2 and 3-4, and adds <1. Since the two trials share reporting (some patients were moved between trials) it's not clear how the new category was added.

RCT of 423 patients with Internet surveys. Medication adherence was only 77% so the true effect of treatment is likely higher. Analysis of primarily low risk patients, authors note the results are not generalizable to the COVID high-risk population. We will update when hearing back on questions asked.

In summary, we believe the results of this study are positive for HCQ being an effective treatment, however we have classified this study as inconclusive for now pending feedback and further analysis.

Also see: [5] and [6] regarding flaws in this study.



[1] twitter.com/Covid19Crusher/status/1284515906375356416

[2] twitter.com/Covid19Crusher/status/1284515906375356416
[3] twitter.com/Covid19Crusher/status/1284515906375356416
[4] frontiersin.org/articles/10.3389/fphar.2020.01062/full
[5] drive.google.com/file/d/1NZOJ57fM0RTaHD1t_9w2iua7lUJhOgWT/view
[6] twitter.com/cnpaiva/status/1303324404630388738

hospitalization, ↓**51.7%**, p=0.19
no recovery, ↓**20.0%**, p=0.21, risk of no recovery at day 14

Source Study Page Submit Corrections or Comments

7/16 **Inconc.**

Early treatment study

***Mitjà** et al., Clinical Infectious Diseases, ciaa1009, doi:10.1093/cid/ciaa1009 (Peer Reviewed)*

Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial

This paper has inconsistent data - some of the values reported in Table 2 and the abstract correspond to 12 control hospitalizations, while others correspond to 11 control hospitalizations.

There was a 25% reduction in hospitalization and 16% reduction in the median time to symptom resolution for HCQ, without statistical significance due to small samples.

Treatment delay is unknown at this time. They report a delay of up to 120 hours after symptoms plus an additional unspecified delay where medication was provided to patients at the first home visit. We have asked for details of the treatment delay and will update when hearing back. They do not break down results by treatment delay.

The paper does not mention zinc. Zinc deficiency in Spain has been reported at 83% [1], this may significantly reduce effectiveness. HCQ is a zinc ionophore which increases cellular uptake, facilitating significant intracellular concentrations of zinc, and zinc is known to inhibit SARS-CoV RNA-dependent RNA polymerase activity, and is widely thought to be important for effectiveness with SARS-CoV-2 [2].

Undetectable viral load was changed to 3 log10 copies/mL potentially masking effectiveness. For viral load authors use nasopharyngeal swabs, we note that viral activity in the lung may be especially important for COVID-19, and that research has shown HCQ concentrations can be much higher in the lung compared to plasma [3]. We also note that viral detection by PCR does not equate to viable virus [4]. Accuracy of the tests is not provided.

Nasopharyngeal viral load analysis issues include test unreliability and temporo-spatial differences in viral shedding [5].

293 low-risk patients with no deaths. No serious adverse events. We have asked for more details on the treatment delay and viral load change and will update when hearing back.

Also see this open letter: [6]

[1] mdpi.com/2072-6643/9/7/697
[2] infezmed.it/index.php/article?Anno=2020&numero=2&ArticoloDaVisualizzare=Vo...
[3] ncbi.nlm.nih.gov/pmc/articles/PMC7122276/HCQ
[4] ams.edu.sg/view-pdf.aspx?file=media%5c5556_fi_331.pdf&ofile=Period+of+Infec...
[5] journal.chestnet.org/article/S0012-3692(20)31718-9/fulltext
[6] drive.google.com/file/d/1NZOJ57fM0RTaHD1t_9w2iua7lUJhOgWT/view

hospitalization, ↓**25.0%**, p=0.64
recovery time, ↓**16.7%**, p=0.38

Source Study Page Submit Corrections or Comments

7/15 **Negative**

Late treatment study

Gupta *et al., JAMA Intern. Med., doi:10.1001/jamainternmed.2020.3596 (Peer Reviewed)*

Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US

Analysis of 2215 intensive care unit patients showing no significant differences with this very late stage use of HCQ. HCQ+AZ mortality relative risk RR 0.96, *p*=0.53, HCQ and HCQ+AZ combined RR 1.06, *p*=0.409.

death, ↑**6.0%**, p=0.41

Source Study Page Submit Corrections or Comments

7/14 **Inconc.**

Early treatment study

Chowdhury *et al., Research Square, doi:10.21203/rs.3.rs-38896/v1 (Preprint)*

A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients

Small 116 patient RCT comparing Ivermectin-Doxycycline and HCQ+AZ, not showing a significant difference in time to PCR negative or symptom resolution. Time to symptomatic recovery was 5.93 days for Ivermectin-Doxycycline vs. 6.99 days for HC Q+AZ. Given the long half-life of HCQ and the lack of a loading dose, it may take several days for HCQ to reach therapeutic levels. 10% of HCQ+AZ patients were lost to followup (2x Ivermectin-Doxycycline). There is no comparison with a control group.

Source Study Page Submit Corrections or Comments

7/11 **Negative**

Late treatment study

Lecronier et al., Critical Care, 24:418, 2020, doi:10.1186/s13054-020-03117-9 (Peer Reviewed)

Comparison of hydroxychloroquine, lopinavir/ritonavir, and standard of care in critically ill patients with SARS-CoV-2 pneumonia: an opportunistic retrospective analysis

Retrospective 80 ICU patients, 22 SOC, 20 lopinavir/ritonavir, 38 HCQ. 28 day mortality 24% (HCQ) versus 41% (SOC), a 41% decrease, but not statistically significant due to very small sample sizes. No statistically significant differences found for treatment escalation, ventilator-free days, viral load, or mortality. Authors consider treatment escalation more important than mortality, for unknown reasons.

death, ↓**42.0%**, p=0.24
treatment escalation, ↓**6.0%**, p=0.73
no virological cure, ↓**15.0%**, p=0.61, risk of viral+ at day 7

Source Study Page Submit Corrections or Comments

7/10 **Negative**

Late treatment study

Cravedi et al., American Journal of Transplantation, doi:10.1111/ajt.16185 (Peer Reviewed)

COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium

Analysis of 144 hospitalized kidney transplant patients showing HCQ mortality HR 1.53, p = 0.17. Subject to confounding by indication.

death, ↑**53.0%**, p=0.17

Source Study Page Submit Corrections or Comments

7/10 **Inconc.**

Late treatment study

Chen et al., medRxiv, doi:10.1101/2020.07.08.20148841v1 (Preprint)

A Multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate Coronavirus disease 2019 (COVID-19)

2 very small studies with hospitalized patients in Taiwan.

RCT with 21 treatment and 12 SOC patients. No mortality, or serious adverse effects. Median time to negative RNA 5 days versus 10 days SOC, p=0.4. Risk of PCR+ at day 14, RR 0.76, p = 0.71.

This paper also reports on a small retrospective study with 12 of 28 HCQ patients and 5 of 9 in the control group being PCR- at day 14, RR 1.29, p = 0.7.

no virological cure, ↓**24.0%**, p=0.71
time to viral-, ↓**50.0%**, p=0.40, median time to PCR-

Source Study Page Submit Corrections or Comments

7/9 **Meta**

Early, Late

***Raoult** et al., Preprint (Preprint) (meta analysis - not included in study count)*

Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial: Response to David Spencer (Elsevier)

Updated meta analysis showing significant reductions in mortality and viral shedding. Mortality OR 0.53 [0.4-0.71] for clinical studies, 0.92 big data studies, 18,211 patients. Persistent viral shedding OR 0.47 [0.28-0.79], 4,540 patients.

Source Study Page Submit Corrections or Comments

7/8 **Review**

N/A

***Li** et al., Cell Death & Disease volume 11, doi:10.1038/s41419-020-2721-8 (Review) (Peer Reviewed) (not included in the study count)*

Is hydroxychloroquine beneficial for COVID-19 patients?

Review of the anti-inflammatory, antiviral, and protective vascular effects of CQ and HCQ, noting that HCQ may be preferable for COVID-19 due to fewer side effects.

Source Study Page Submit Corrections or Comments

7/7 **Review**

Review

***Goldstein**, L., Preprint, July 7, 2020 (Review) (Preprint) (not included in the study count)*

Hydroxychloroquine-based COVID-19 Treatment, A Systematic Review of Clinical Evidence and Expert Opinion from Physicians' Surveys

85% of globally surveyed physicians recognized HCQ as at least partially effective in treating COVID-19, according to Sermo W3. More than half of the surveyed US

physicians would take the drug or give it to family members early or even before onset of symptoms, according to JC.

Aside from the rarely used plasma, HCQ / HCQ+AZ based treatments are preferred by physicians by wide margin over other drugs. HCQ / HCQ+AZ based treatments are the most used, most recommended, and most highly rated by physicians treating COVID-19 at an early stage.

Source Study Page Submit Corrections or Comments

7/7 **Negative**

Late treatment study

An *et al., medRxiv, doi:10.1101/2020.07.04.20146548 (Preprint)*

Treatment Response to Hydroxychloroquine and Antibiotics for mild to moderate COVID-19: a retrospective cohort study from South Korea

Retrospective of hospitalized patients with 31 HCQ patients and 195 standard treatment patients, not showing a significant difference in terms of viral clearance or recovery. There was no mortality in either group.

"It is notable that HQ plus antibiotics group had worse baseline clinical profiles (i.e. higher percentage of moderate severity patients, more patients with fever >=37.5C, higher average body temperature) and prognostic indicators such as age, LDH, lymphocyte count, and CRP".

We note that propensity score matching removed almost all of the male patients in the control group (40% -> 5%) but increased the percentage of male patients in the treatment group. This provides a large advantage to the control group because there is a very large difference in severity and mortality based on gender [1].

In terms of viral RNA clearance we note that other research has found that "active viral replication drops quickly after the first week, and viable virus was not found after the second week of illness despite the persistence of PCR detection of RNA" [2].

[1] ncbi.nlm.nih.gov/pmc/articles/PMC7247289/
[2] ams.edu.sg/view-pdf.aspx?file=media%5c5556_fi_331.pdf&ofile=Period+of+Infec...

no virological cure, ↓**3.0%**, p=0.92, time to viral clearance

Source Study Page Submit Corrections or Comments

7/3 **Positive**

Pre-Exposure Prophylaxis study

Zhong *et al., Lancent Rheumatology, 10.1016/S2665-9913(20)30227-7 (Peer Reviewed)*

COVID-19 in patients with rheumatic disease in Hubei province, China: a multicentre retrospective observational study

Rheumatic disease patients on HCQ had a lower risk of COVID-19 than those on other disease-modifying anti-rheumatic drugs, OR 0.09 (0.01–0.94), *p*=0.044 after adjusting for age, sex, smoking, systemic lupus erythematosus, infection in other family members, and comorbidities. 43 patients with rheumatic disease and COVID-19 exposure.

COVID-19 case, ↓**91.0%**, p=0.04

Source Study Page Submit Corrections or Comments

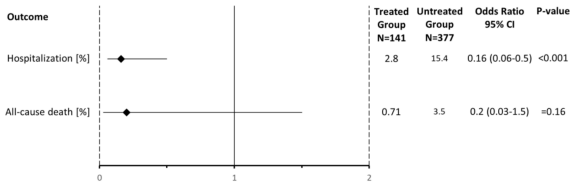
7/3 **Positive**

Early treatment study

Scholz *et al., Preprints 2020, 2020070025, doi:10.20944/preprints202007.0025.v1 (Preprint)*

COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study

Early treatment with HCQ+AZ+Z results in 84% lower hospitalization and 80% lower death - hospitalization OR 0.16 (*p*<0.001), death OR 0.2 (*p*=0.16). No cardiac side effects. Retrospective 518 patients (141 treated, 377 control).



death, ↓**79.4%**, p=0.13
hospitalization, ↓**81.6%**, p<0.001

Source Study Page Submit Corrections or Comments

7/1 **Positive**

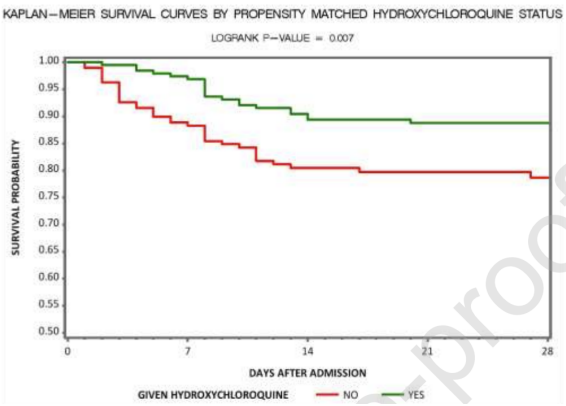
Late treatment study

Arshad *et al., Int. J. Infect. Dis., July 1 2020, doi:10.1016/j.ijid.2020.06.099 (Peer Reviewed)*

Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19

HCQ decreases mortality from 26.4% to 13.5% (HCQ) or 20.1% (HCQ+AZ). Propensity matched HCQ HR 0.487, *p*=0.009. Michigan 2,541 patients retrospective. Before propensity matching the HCQ group average age is 5 years younger and the percentage of male patients is 4% higher which is likely to favor the treatment and the control respectively in the before-propensity matching results.

Some reported limtiations of this study are inaccurate [1]. Corticosteroids were controlled for in the multivariate and propensity analyses as were age and comorbidities including cardiac disease and severity of illness. Age was an independent risk factor associated with mortality. HCQ was independently associated with decreased mortality, distinct from the steroid effect. 91% of all patients began treatment within two days of admission. HCQ was used throughout the study period, limiting time bias. Patients assigned to HCQ group had moderate and severe illness at presentation, which would favor worse outcome with HCQ.



[1] ijidonline.com/article/S1201-9712(20)30604-4/fulltext

death, ↓51.3%, p=0.009

Source Study Page Submit Corrections or Comments

7/1 **Safety**

N/A

Samuel et al., Heart Rhythm, doi:10.1016/j.hrthm.2020.06.033 (Peer Reviewed) (not included in the study count)

Incidence of arrhythmias and electrocardiographic abnormalities in symptomatic pediatric patients with PCR positive SARS-CoV-2 infection including drug induced changes in the corrected QT interval (QTc)

In pediatric patients with PCR positive active COVID-19 infection, significant arrhythmias are infrequent, but occur at an incidence higher than expected in a general pediatric population. Comorbidities are not more common in patients with arrhythmias than in patients without arrhythmias. However, providers still need to be vigilant for comorbidities that may independently place patients at risk for arrhythmias. COVID-19 treatment using HCQ leads to significant QTc prolongation, but was not associated with arrhythmias in pediatric patients. The long term sequelae of arrhythmia development in this population and their impact on outcome needs to be studied.

Source Study Page Submit Corrections or Comments

6/30	**Positive**	Late treatment study *Martinez-Lopez et al., (Preprint)* Multiple Myeloma and SARS-CoV-2 Infection: Clinical Characteristics and Prognostic Factors of Inpatient Mortality Retrospective 167 multiple myeloma patients in Spain death, ↓**33.0%**, p=0.20 Source Study Page Submit Corrections or Comments
6/30	**Positive**	Late treatment study *Mikami et al., J. Gen. Intern. Med., doi:10.1007/s11606-020-05983-z (Peer Reviewed)* Risk Factors for Mortality in Patients with COVID-19 in New York City HCQ decreases mortality, HR 0.53 (CI 0.41–0.67). IPTW adjustment does not significantly change HR 0.53 (0.41-0.68). Retrospective 6,000 patients in New York City. death, ↓**47.0%**, p<0.0001 Source Study Page Submit Corrections or Comments
6/30	**Negative**	Late treatment study *Komissarov et al., medRxiv, doi:10.1101/2020.06.30.20143289 (Preprint)* Hydroxychloroquine has no effect on SARS-CoV-2 load in nasopharynx of patients with mild form of COVID-19 Small late stage (7-10 days post symptoms) study of nasal swab RNA with 12 control and 33 patients, showing no significant differences (significant reduction in viral load is seen in both groups). The groups are not comparable, with significant differences seen between hospitalized and non-hospitalized patients. 9 of 10 hospitalized patients were in the HCQ group and only one in the control group. 2 additional control patients were added between the first and second version of this preprint (including the only hospitalized control patient). viral load, ↑**25.0%**, p=0.45 Source Study Page Submit Corrections or Comments

6/29	**Positive**	Pre-Exposure Prophylaxis study *Ferreira et al., J. Medical Virology, July 9, 2020, doi:10.1002/jmv.26286 (preprint 6/29) (Peer Reviewed)* Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection Chronic treatment with HCQ provides protection against COVID, odds ratio 0.51 (0.37-0.70). The actual benefit is likely to be larger becasue research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall. Ferri et al. show OR 4.42, $p<0.001$ [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure. [1] c19study.com/ferri.html COVID-19 case, ↓**47.1%**, p<0.0001 (odds ratio converted to relative risk) Source Study Page Submit Corrections or Comments
6/29	**Safety**	N/A *Mfeukeu-Kuate et al. (Preprint) (not included in the study count)* Electrocardiographic safety of daily Hydroxychloroquine 400mg plus Azithromycin 250mg as an ambulatory treatment for COVID-19 patients in Cameroon No life-threatening modifications of the QT interval was observed in non-severe COVID-19 patients treated ambulatory with HCQ+AZ. 51 relatively young patients 39 +/- 11. Source Study Page Submit Corrections or Comments
6/25	**Inconc.**	Pre-Exposure Prophylaxis study *Gendebien et al., Annals of the Rheumatic Diseases, doi:10.1136/annrheumdis-2020-218244 (Letter)* Systematic analysis of COVID-19 infection and symptoms in a systemic lupus erythematosus population: correlation with disease characteristics, hydroxych loroquine use and immunosuppressive treatments Small study of 152 SLE patients taking HCQ with a phone survey for COVID-19

suggestive symptoms. There was 2 hospitalizations (group not identified) and no ICU or death cases. A similar percentage of suspected infections were reported for HCQ users and non-HCQ users, RR 0.96, *p* = 0.93.

There was no mortality and severity was not analyzed to determine if HCQ treated patients fared better. No adjustment for concomitant medications or severity of SLE. Only 5 cases were PCR confirmed.

COVID-19 case, ↓**3.9%**, p=0.93

Source Study Page Submit Corrections or Comments

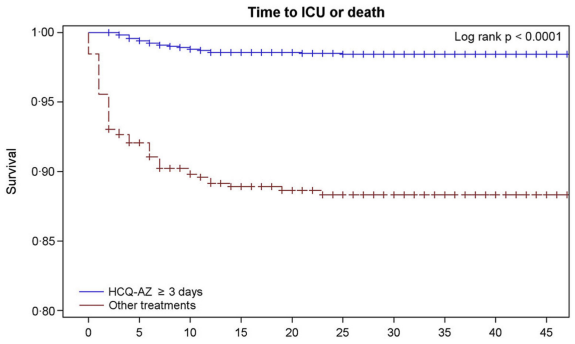
6/25 **Positive**

Early treatment study

Lagier *et al., Travel Med. Infect. Dis. 101791, Jun 25, 2020, doi:10.1016/j.tmaid.2020.101791 (Peer Reviewed)*

Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis

Early treatment leads to significantly better clinical outcome and faster viral load reduction. Matched sample mortality HR 0.41 p-value 0.048. Retrospective 3,737 patients.



death, ↓**59.0%**, p=0.05

Source Study Page Submit Corrections or Comments

6/23 **Positive**

Late treatment study

Bousquet *et al., Aging, 12:12, 11306-11313, doi:10.18632/aging.103583 (Peer Reviewed)*

ADL-dependency, D-Dimers, LDH and absence of anticoagulation are independently associated with one-month mortality in older inpatients with Covid-19

Observational prospective 108 hospitalized patients 65 and older, showing HCQ mortality OR 0.49, p = 0.15.

death, ↓**42.8%**, p=0.15
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

6/22 **Positive**

Late treatment study

Fontana *et al., Clinical Kidney Journal, 13:3, 334–339, doi:10.1093/ckj/sfaa084 (Peer Reviewed)*

SARS-CoV-2 infection in dialysis patients in northern Italy: a single-centre experience

Very small observational study of 15 dialysis patients showing HCQ mortality RR 0.50, p = 0.53.

death, ↓**50.0%**, p=0.53

Source Study Page Submit Corrections or Comments

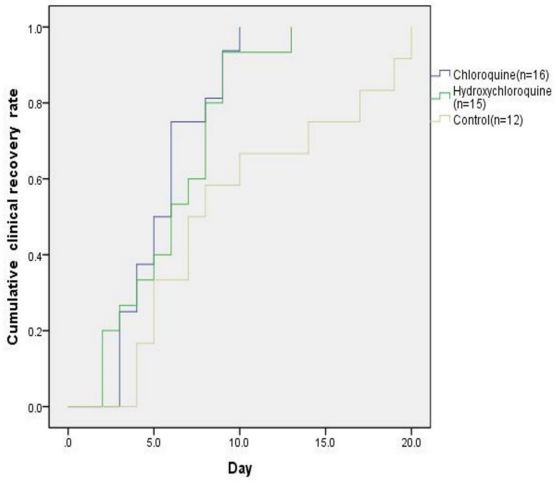
6/22 **Positive**

Early treatment study

Chen *et al., medRxiv, doi:10.1101/2020.06.19.20136093 (Preprint)*

Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study

Significantly faster clinical recovery and shorter time to RNA negative (from 7.0 days to 2.0 days (HCQ), p=0.01. 67 patients with mild/moderate cases.

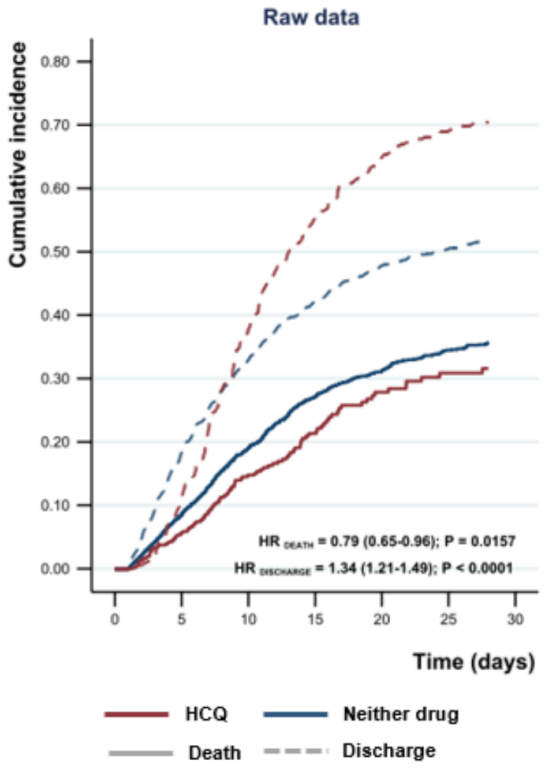


		time to viral-, ↓**72.0%**, p=0.01, median time to PCR- Source Study Page Submit Corrections or Comments
6/21	**Inconc.**	Late treatment study ***Faico-Filho*** *et al., medRxiv, doi:10.1101/2020.06.16.20133066 (Preprint)* Effect of hydroxychloroquine on SARS-CoV-2 viral load in patients with COVID-19 Viral load comparison for 34 HCQ and 32 control patients hospitalized with moderate COVID-19. All patients recovered limiting the room for beneficial effects. While not achieving statistical significance, results show faster recovery with HCQ - in Table 2 Δt 7-12 shows much faster recovery for HCQ use (ΔCt ~11 versus 6). Source Study Page Submit Corrections or Comments
6/19	**Positive** (news)	Pre-Exposure Prophylaxis study ***SMSH*** *Sawai Man Singh Hospital, India (News) (not included in the study count)* HCQ beneficial as preventive drug: SMS doctors told ICMR PrEP with 4,300 very high risk healthcare workers in a hospital with up to 500+ COVID patients at a time, only 1% cases, all recovered. Currently no formal study is available so this is not included in the study count. Source Study Page Submit Corrections or Comments
6/19	**Negative** (news)	Late treatment study ***NIH****, study not available yet (News) (not included in the study count)* NIH halts clinical trial of hydroxychloroquine NIH halts late stage trial reporting no harm and no benefit. 470 patients. Currently no formal study is available so this is not included in the study count. Source Study Page Submit Corrections or Comments
6/19	**Positive**	Late treatment study ***Sbidian*** *et al., medRxiv, doi:10.1101/2020.06.16.20132597 (Preprint)*

Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France

Retrospective of 4,642 hospitalized patients in France showing significantly faster discharge with HCQ and HCQ+AZ. No significant effect is seen on 28-day mortality, however many more control patients are still in hospital at 28 days. Other studies show faster resolution for HCQ, suggesting there will be a significant improvement when extending past 28 days. Hopefully authors will extend the analysis. Note that the median age is higher in the group not treated with HCQ or AZ.

For other issues with the adjustments see [1]. Also see the analysis here [2].



[1] medrxiv.org/content/10.1101/2020.06.16.20132597v1#disqus_thread
[2] twitter.com/Covid19Crusher/status/1274668697408471040

death, ↑5.0%, p=0.74
no hospital discharge, ↓20.0%, p=0.002

Source Study Page Submit Corrections or Comments

6/18 **Inconc.**

Late treatment study

***Paccoud** et al., Clinical Infectious Diseases, doi:10.1093/cid/ciaa791 (Peer Reviewed)*

Compassionate use of hydroxychloroquine in clinical practice for patients with mild to

severe Covid-19 in a French university hospital

Retrospective of 89 hospitalized patients, survival HR 0.89 [0.23-3.47], not statistically significant. Authors note that unmeasured confounders may have persisted and the study may be underpowered.

death, ↓**11.0%**, p=0.88

Source Study Page Submit Corrections or Comments

6/17 **Positive**

Late treatment study

***Xue** et al., J. Med. Virology, June 17, 2020, doi:10.1002/jmv.26193 (Peer Reviewed)*

Hydroxychloroquine treatment in COVID-19: a descriptive observational analysis of 30 cases from a single center in Wuhan, China

30 hospitalized patients. Early use of HCQ is more effective, 43% reduction in progression from moderate to severe. "Early" is relative here, within 7 days of hospitalization.

Source Study Page Submit Corrections or Comments

6/17 **Inconc.**

Late treatment study

***Luo** et al., Annals of Oncology, 31:10, 1386-1396, doi:10.1016/j.annonc.2020.06.007 (Peer Reviewed)*

COVID-19 in patients with lung cancer

Analysis of hospitalized lung cancer patients with 35 of 48 taking HCQ, mortality OR 1.03, p = 0.99.

death, ↑**2.2%**, p=0.99
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

6/16 **Inconc.**

Late treatment study

***Kim** et al., Korean J Intern Med, doi:10.3904/kjim.2020.224 (Peer Reviewed)*

Lopinavir-ritonavir versus hydroxychloroquine for viral clearance and clinical improvement in patients with mild to moderate coronavirus disease 2019

Small retrospective study of hospitalized patients with 31 lopinavir-ritonavir and 34

HCQ patients, HCQ 400mg once per day, finding no significant difference in clinical response, but more rapid viral clearance with lopinavir-ritonavir.

Source Study Page Submit Corrections or Comments

6/16 **Positive** (news)

Pre-Exposure Prophylaxis study

WHIP *COVID-19 (News) (not included in the study count)*

Henry Ford Health System still moving forward with hydroxychloroquine study

Ongoing WHIP COVID-19 HCQ PrEP study reports analyzing their data and seeing a significantly improved outcome in a group of COVID-19 patients who received HCQ. For more details on the study see [1]. Currently no formal study is available so this is not included in the study count.

[1] henryford.com/whip-covid-19

Source Study Page Submit Corrections or Comments

6/16 **Positive**

Pre-Exposure Prophylaxis study

Huang *et al., Annals of the Rheumatic Diseases 2020:79, 1163-1169, doi:10.1136/annrheumdis-2020-217425 (Peer Reviewed)*

Clinical characteristics of 17 patients with COVID-19 and systemic autoimmune diseases: a retrospective study

Analysis of 1255 COVID-19 patients in Wuhan Tongji Hospital finding 0.61% with systemic autoimmune diseases, much lower than authors expected (3%–10%). Authors hypothesise that protective factors, such as CQ/HCQ use, reduce hospitalization.

hospitalization, ↓80.0%, p<0.001

Source Study Page Submit Corrections or Comments

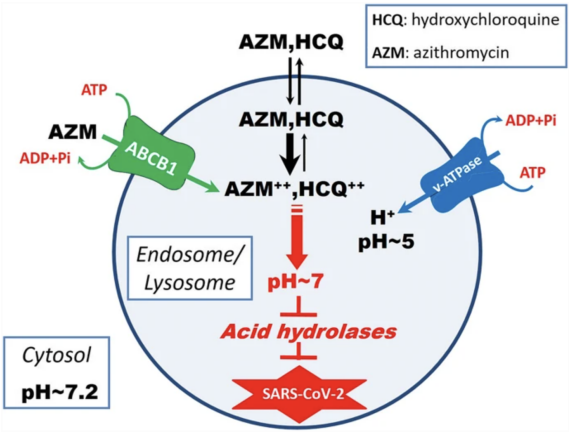
6/12 **Theory**

Theory

Scherrmann, AAPS J 22, 86 (2020), doi:10.1208/s12248-020-00465-w (Peer Reviewed) (Theory) (not included in the study count)

Intracellular ABCB1 as a Possible Mechanism to Explain the Synergistic Effect of Hydroxychloroquine-Azithromycin Combination in COVID-19 Therapy

Theory paper, not included in the study count or percentages. Proposes a new mechanism supporting the synergistic interaction between HCQ+AZ.



Source Study Page Submit Corrections or Comments

6/12 **Negative**

Late treatment study

Giacomelli et al., Journal of Medical Virology, doi:10.1002/jmv.26407 (preprint 6/12) (Peer Reviewed)

Early administration of lopinavir/ritonavir plus hydroxychloroquine does not alter the clinical course of SARS-CoV-2 infection: a retrospective cohort study

Late stage study of hospitalized patients comparing treatment starting within 5 days versus later. Note that "early" here is only relative - all patients are hospitalized so this is "late" and "very late". The "early" treatment group is significantly older. Severe adverse events attributed by authors to concurrent administration of LPV, making it difficult to make conclusions about HCQ.

Source Study Page Submit Corrections or Comments

6/10 **Inconc.**

Late treatment study

Wang et al., medRxiv, doi:10.1101/2020.06.11.20128926 (Peer Reviewed)

Comorbidity and Sociodemographic determinants in COVID-19 Mortality in an US Urban Healthcare System

Database analysis of 7,592 patients in NYC, showing adjusted HCQ mortality odds ratio OR 0.96, p = 0.82, and HCQ+AZ OR 0.94, p = 0.63

death, ↓**5.8%**, p=0.63
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

6/10 **Positive**

Early treatment study

Otea et al., medRxiv, doi:10.1101/2020.06.10.20101105 (Preprint)

A short therapeutic regimen based on hydroxychloroquine plus azithromycin for the treatment of COVID-19 in patients with non-severe disease. A strategy associated with a reduction in hospital admissions and complications.

80 moderate cases, HCQ+AZ appears to reduce serious complications and death. Moderate treated cases resulted in hospitalization at the same rate as mild untreated cases suggesting efficacy.

Source Study Page Submit Corrections or Comments

6/9 **Positive**

Early treatment study

Pirnay et al., Hosp. Pharm. and Clinician, doi:10.1016/j.phclin.2020.06.001 (Peer Reviewed)

Beneficial effect of Hydroxychloroquine-Azithromycin combination in the treatment of elderly patients with Covid-19: results of an observational study

68 very high risk nursing home residents, median age 86, HCQ+AZ early treatment within 2.5 days onset, 2 stopped due to QTc. Only 7 died, significantly less than other nursing homes in France and the same as the median death for the same period in 2019/2018.

Source Study Page Submit Corrections or Comments

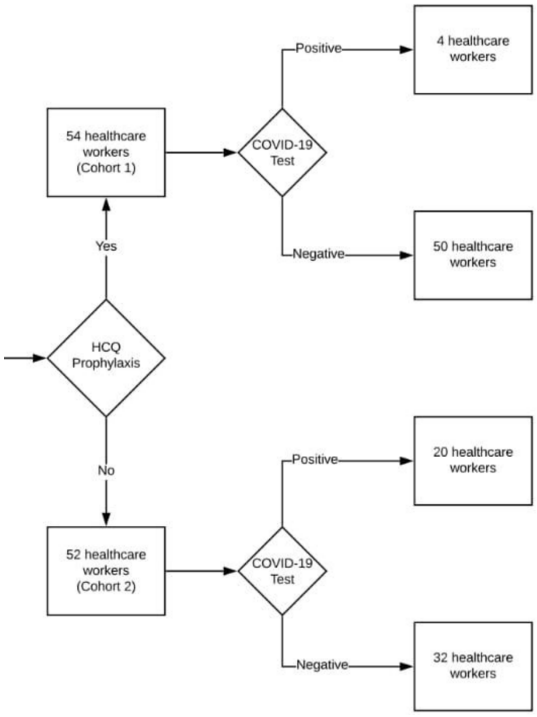
6/9 **Positive**

Pre-Exposure Prophylaxis study

Bhattacharya et al., medRxix, doi:10.1101/2020.06.09.20116806 (Preprint)

Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers

HCQ reduced cases from 38% to 7%. 106 people. No serious adverse effects.



COVID-19 case, ↓**80.7%**, p=0.001

Source Study Page Submit Corrections or Comments

6/6 **Review**

Review

***Roussel** et al., New Microbes and New Infections, Volume 38, doi:10.1016/j.nmni.2020.100710 (Review) (Peer Reviewed) (not included in the study count)*

Influence of conflicts of interest on public positions in the COVID-19 era, the case of Gilead Sciences

Shows a correlation (Spearman test, p = 0.017) between the amount received from Gilead Sciences and public opposition to the use of HCQ in France.

Position towards HCQ	Number	Average (€)
Very favourable	8	52
Favourable	6	1524
Neutral	14	9729
Unfavourable	7	11 085
Very Unfavourable	9	24 048
Did not take position	54	4421
Total	98	6924

Source Study Page Submit Corrections or Comments

6/6 **Meta**

Early, Late

Million *et al., New Microbes and New Infections, doi:10.1016/j.nmni.2020.100709 (Peer Reviewed) (meta analysis - not included in study count)*

Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative metaanalysis between the Big data and the real world

[H]CQ effective and reduces mortality by a factor 3. Meta analysis of 20 studies.

Outcome	Country	Study name	Statistics for each study			
			Odds ratio	Lower limit	Upper limit	p-Value
K. Death or ICU transfer	Iran	Ali Ashraf, MedRxiv, 2020	0.04	0.01	0.17	0.000031
A. Hospitalization rate	Brazil	Barbosa Esper, 2020	0.35	0.14	0.87	0.023675
I. Aggravation to severe	China	Chen, J Zheijang Univ, 2020 RCT	3.21	0.12	85.20	0.486189
H. Thoracic CT-scan imaging	China	Chen, J Zheijang Univ, 2020 RCT	1.75	0.40	7.66	0.457708
N. Persistent viral shedding	China	Chen, J Zheijang Univ, 2020 RCT	2.15	0.17	26.67	0.550103
I. Aggravation to severe	China	Chen, MedRxiv, 2020 RCT	0.10	0.00	1.88	0.123172
H. Thoracic CT-scan imaging	China	Chen, MedRxiv, 2020 RCT	0.29	0.09	0.91	0.033657
C. Duration of fever	China	Chen, MedRxiv, 2020 RCT	0.14	0.04	0.46	0.001441
B. Duration of cough	China	Chen, MedRxiv, 2020 RCT	0.13	0.03	0.45	0.001493
K. Death or ICU transfer	France	Davido, MedRxiv, 2020	0.41	0.21	0.80	0.008863
N. Persistent viral shedding	France	Gautret, Int J Antimicrob Agents, 2020 with AZ	0.01	0.00	0.32	0.007603
N. Persistent viral shedding	France	Gautret, Int J Antimicrob Agents, 2020 without AZ	0.11	0.02	0.66	0.016207
I. Death	France	Guerin, 2020	0.54	0.03	14.01	0.713884

Source Study Page Submit Corrections or Comments

6/5 **Negative**

Late treatment study

RECOVERY *Collaborative Group, NEJM, doi:10.1056/NEJMoa2022926 (press release 6/5) (Preprint)*

Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial

RECOVERY trial finds no significant benefit for very late stage very sick patients. Results may be due to the unusually high dosage used (9.2g total over 10 days) [1, 2].

The overall dosage used is only 23% less than the high dosage that Borba et al. show greatly increases risk (OR 2.8) [3].

Authors do not report results based on weight, BMI, or related conditions such as diabetes, which may provide additional evidence of toxic dosages. Authors do not adjust dosage based on patient weight, so toxicity may be higher in patients of lower weight.

KM curves show a spike in HCQ mortality days 5-8, corresponding to ~85% of the total excess seen at day 28 (a similar spike is seen in the SOLIDARITY trial).

Authors will not release the data until Jan 8, 2021.

Authors note: "we did not observe excess mortality in the first 2 days of treatment ... when early effects of dose-dependent toxicity might be expected", but they are ignoring the very long half-life of HCQ and the dosing regimen - much higher levels of HCQ will be reached later. Increased mortality in Borba et al. occurred after 2 days.

Patients were extremely sick (median 9 days post symptoms, 60% requiring oxygen and an additional 17% requiring ventilation/ECMO), and an unusually high death rate was seen in both arms. 1,561 HCQ patients, 3,155 SOC.

A secondary analysis has found several inconsistencies in the data: [4]. Hypoxia may inhibit HCQ entering cells [5], making it less effective for late stage use.

[1] twitter.com/JamesTodaroMD/status/1272661099985481733
[2] twitter.com/JamesTodaroMD/status/1276245669372723200
[3] c19study.com/borba.html
[4] francesoir.fr/politique-monde/oxford-etude-recovery-ou-sont-les-morts
[5] twitter.com/JaclynHord/status/1302704076573077507

death, ↑**9.0%**, p=0.15

Source Study Page Submit Corrections or Comments

6/3 **Positive** (see notes)

Post Exposure Prophylaxis study

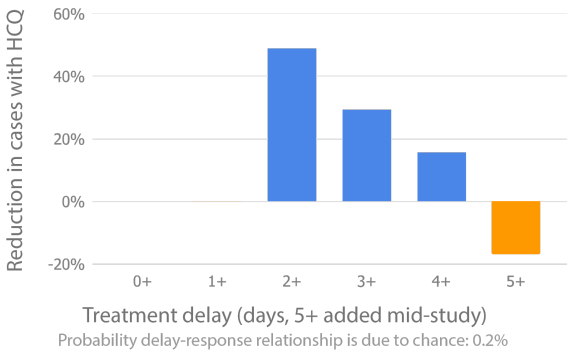
***Boulware** et al., NEJM, June 3 2020, doi:10.1056/NEJMoa2016638 (Peer Reviewed)*

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

COVID-19 cases are reduced by [49%, 29%, 16%] respectively when taken within ~[70, 94, 118] hours of exposure (including shipping delay). The treatment delay-response relationship is significant at *p*=0.002. PEP delayed treatment RCT.

Currently this is the only study where we have evaluated the result as positive while the authors indicate it is negative. We provide a detailed explanation of why the results presented here are positive [1]. Note that author comments also differ from the published conclusion.

6 independent analyses confirm efficacy: [2, 3, 4, 5, 6, 7, 8].



[1] c19study.com/boulware.html
[2] drive.google.com/file/d/1NZOJ57fM0RTaHD1t_9w2iua7lUJhOgWT/view
[3] arxiv.org/abs/2007.09477
[4] medrxiv.org/content/10.1101/2020.08.19.20178376v1
[5] researchgate.net/publication/344369617_Hydroxychloroquine_as_Post-Exposure...
[6] blog.philbirnbaum.com/2020/08/the-nejm-hydroxychloroquine-study-fails.html
[7] longdom.org/open-access/hydroxychloroquine-and-interferons-for-the-prophylax...
[8] osf.io/vz8a7/

COVID-19 case, ↓**17.0%**, p=0.35
COVID-19 case, ↓**25.1%**, p=0.22, probable COVID-19 case

Source Study Page Submit Corrections or Comments

N/A

Al-Kofahi *et al., Clin. Pharmacol. Ther., Jun 1, 2020, doi:10.1002/cpt.1874 (Peer Reviewed) (not included in the study count)*

Finding the Dose for Hydroxychloroquine Prophylaxis for COVID-19: The Desperate Search for Effectiveness

6/1 **Dosing**

Analysis of HCQ dosing regimens, recommending:

PrEP: 800mg loading dose followed by 400mg 2 or 3 times weekly to maintain weekly troughs above EC_{50} in >50% of patients at steady-state.

PEP: 800mg loading dose followed in 6 hours by 600mg, then 600mg daily for 4 more days to achieve daily troughs above EC_{50} in >50% subjects.

Source Study Page Submit Corrections or Comments

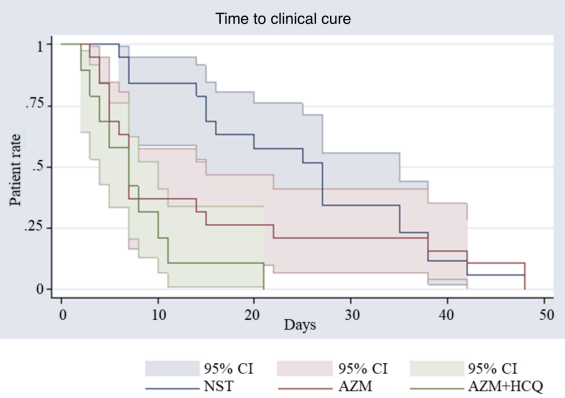
5/31 **Positive**

Early treatment study

Guérin et al., Asian J. Medicine and Health, July 15, 2020, doi:10.9734/ajmah/2020/v18i730224 (preprint 5/31) (Peer Reviewed)

Azithromycin and Hydroxychloroquine Accelerate Recovery of Outpatients with Mild/Moderate COVID-19

Mean clinical recovery time reduced from 26 days (SOC) to 9 days, $p<0.0001$ (HC Q+AZ) or 13 days, $p<0.0001$ (AZ). No cardiac toxicity. Small retrospective study of 88 patients with case control analysis with matched patients.



death, ↓**43.0%**, p=0.73
recovery time, ↓**65.0%**, p<0.0001

Source Study Page Submit Corrections or Comments

Late treatment study

Chamieh et al., medRxiv 2020.05.28.20114835, doi:10.1101/2020.05.28.20114835 (Preprint)

5/28 **Positive**

Viral Dynamics Matter in COVID-19 Pneumonia: the success of early treatment with hydroxychloroquine and azithromycin in Lebanon

HCQ+AZ potentially explains 94.7% success in treating a fairly complex cohort.

Source Study Page Submit Corrections or Comments

5/28 **Positive**

Pre-Exposure Prophylaxis study

Chatterjee et al., Indian J. Med. Res., June 20, 2020, doi:10.4103/ijmr.IJMR_2234_20 (Peer Reviewed)

Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19

4+ doses of HCQ associated with a significant decline in the odds of getting infected, dose-response relationship exists.

COVID-19 case, ↓**66.8%**, p<0.001, full course vs. unused risk of COVID-19 case

Source Study Page Submit Corrections or Comments

5/28 **Positive**

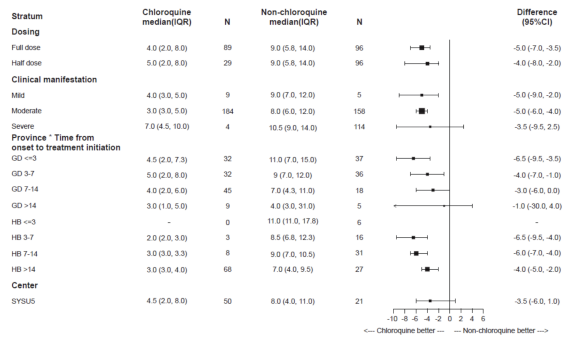
Late treatment study

Huang *et al., National Science Review, nwaa113, doi:10.1093/nsr/nwaa113 (Peer Reviewed)*

Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19

197 CQ patients, 176 control. Mean time to undetectable viral RNA and duration of fever significantly reduced. No serious adverse events.

Figure 3. Post hoc analysis on the effect of chloroquine on time to undetectable viral RNA by stratification.



time to viral-, ↓**67.0%**, p<0.0001

Source Study Page Submit Corrections or Comments

5/27 **Inconc.**

Late treatment study

Goldman *et al., NEJM, doi:10.1056/NEJMoa2015301 (Peer Reviewed)*

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Study focused on remdesivir but with results for HCQ in the supplementary appendix, showing 9% death with HCQ versus 12% control, unadjusted relative risk uRR 0.78, *p* = 0.46.

death, ↓**22.3%**, p=0.46

Source Study Page Submit Corrections or Comments

5/28	**Negative**	Late treatment study *Kuderer et al., Lancet, June 20, 2020, doi:10.1016/S0140-6736(20)31187-9 (preprint 5/28) (Peer Reviewed)* Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study Retrospective 928 cancer patients, showing HCQ OR 1.06 [0.51-2.20]. HCQ+AZ OR 2.93 [1.79-4.79]. The relative risks of different therapies suggest that the results are overly affected by confounding by indication. Authors note: HCQ+AZ might not be the cause of increased mortality, but instead these were given to patients with more severe COVID-19. death, ↑**134.2%**, p<0.0001 (odds ratio converted to relative risk) Source Study Page Submit Corrections or Comments
5/28	**Inconc.**	Pre-Exposure Prophylaxis study *Gianfrancesco et al., Annals of the Rheumatic Diseases, 79:7, 859-866, doi:10.1136/annrheumdis-2020-217871 (Peer Reviewed)* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry Analysis of rheumatic disease patients showing no significant association between antimalarial therapy and hospitalisation, OR=0.94 [0.57-1.57], *p*=0.82 after adjustments. hospitalization, ↓**3.3%**, p=0.82 (odds ratio converted to relative risk) Source Study Page Submit Corrections or Comments
5/27	**Meta**	Early treatment study *Risch, American Journal of Epidemiology, kwaa093, 27 May 2020, doi:10.1093/aje/kwaa093 (Peer Reviewed) (meta analysis - not included in study count)* Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis Five studies, including two controlled clinical trials, have demonstrated significant outpatient treatment efficacy.

Source Study Page Submit Corrections or Comments

5/25 **Negative**

Late treatment study

Ip et al., medRxiv, doi:10.1101/2020.05.21.20109207 (Preprint)

Hydroxychloroquine and Tocilizumab Therapy in COVID-19 Patients - An Observational Study

Retrospective study of late stage use on 2,512 hospitalized patients showing no significant differences in associated mortality for patients receiving any HCQ during the hospitalization (HR, 0.99 [95% CI, 0.80-1.22]), HCQ alone (HR, 1.02 [95% CI, 0.83-1.27]), or HCQ+AZ (HR, 0.98 [95% CI, 0.75-1.28]). Misclassification is possible due to manual abstraction of EHR data. They observed a change in the prescribing patterns of HCQ during the study timeframe. Confounding by indication.

death, ↓**1.0%**, p=0.93

Source Study Page Submit Corrections or Comments

5/22 **Positive** (advisory)

PEP, PrEP

ICMR, Indian Council of Medical Research (Advisory) (not included in the study count)

Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for SARS-CoV-2 infection

Healthcare workers on HCQ prophylaxis less likely to get COVID. Significant dose-response relationship. Extends recommended HCQ prophylaxis to asymptomatic household contacts of cases and frontline workers. Degree of benefit not quantified. Currently no formal study is available so this is not included in the study count.

1.3 Studies on prophylaxis of SARS-CoV-2 infection

- A retrospective case-control analysis at ICMR has found that there is a significant dose-response relationship between the number of prophylactic doses taken and frequency of occurrence of SARS-CoV-2 infection in symptomatic healthcare workers who were tested for SARS-CoV-2 infection.
- Another investigation from 3 central government hospitals in New Delhi indicates that amongst healthcare workers involved in COVID-19 care, those on HCQ prophylaxis were less likely to develop SARS-CoV-2 infection, compared to those who were not on it. The benefit was less pronounced in healthcare workers caring for a general patient population.
- An observational prospective study of 334 healthcare workers at AIIMS, out of which 248 took HCQ prophylaxis (median 6 weeks of follow up) in New Delhi also showed that those taking HCQ prophylaxis had lower incidence of SARS-CoV-2 infection than those not taking it.

Source Study Page Submit Corrections or Comments

5/22 **Retracted**

Late treatment study

Mehra et al., The Lancet, May 22, 2020, doi: 10.1016/S0140-6736(20)31180-6 (Peer Reviewed) (not included in the study count)

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Incorrect at first read (implausible death, ventilation, and population numbers). This paper was retracted.

Source Study Page Submit Corrections or Comments

5/19 **Negative**

Late treatment study

Singh et al., medRxiv, doi:10.1101/2020.05.12.20099028 (Preprint)

Outcomes of Hydroxychloroquine Treatment Among Hospitalized COVID-19 Patients in the United States- Real-World Evidence From a Federated Electronic Medical Record Network

EHR analysis of 3,372 hospitalized COVID-19 patients not showing a significant difference for mortality or the risk of mechanical ventilation. Subject to the limitations of EHR analysis. Misclassification is possible. Confounding by indication.

death, ↓**5.0%**, p=0.72
ventilation, ↓**19.0%**, p=0.26

Source Study Page Submit Corrections or Comments

5/18 **Positive**

Late treatment study

Kim et al., medRxiv, doi:10.1101/2020.05.13.20094193 (Preprint)

Treatment Response to Hydroxychloroquine, Lopinavir/Ritonavir, and Antibiotics for Moderate COVID 19: A First Report on the Pharmacological Outcomes from South Korea

Retrospective of 97 moderate cases. Time to viral clearance significantly shorter for HCQ+antibiotic. Preprint withdrawn pending peer review.

hospitalization time, ↓**51.0%**, p=0.01
time to viral-, ↓**56.0%**, p=0.005

Source Study Page Submit Corrections or Comments

5/18 **Positive**

Early treatment study

Ahmad et al., doi:10.1101/2020.05.18.20066902 (Preprint)

Doxycycline and Hydroxychloroquine as Treatment for High-Risk COVID-19 Patients: Experience from Case Series of 54 Patients in Long-Term Care Facilities

54 patients in long term care facilities. 6% death with HCQ+AZ compared to 22% using a naive indirect comparison.

Source Study Page Submit Corrections or Comments

Pre-Exposure Prophylaxis study

Macias et al., medRxiv, 10.1101/2020.05.16.20104141 (Preprint)

Similar incidence of Coronavirus Disease 2019 (COVID-19) in patients with rheumatic diseases with and without hydroxychloroquine therapy

Very small retrospective study of rheumatic disease patients, sample size is too small for statistical significance (HCQ 0.5-4.0%, no-HCQ 0.4-2.7%). Confirmed cases were 1 HCQ and 2 no-HCQ, confirmed+likely cases were 1 HCQ and 3 no-HCQ. 1 HCQ and 2 no-HCQ patients were admitted to hospital. We do not think a conclusion can be drawn based on these sample sizes.

5/16 **Inconc.**

There are very significant differences between the groups, for example 30% of the HCQ group have SLE vs. 2.5% of the no-HCQ group. SLE patients have a 5.7 times relative risk of pneumonia according to [1], whereas the relative risk with glucocorticoids and TNF-α inhibitors is significantly lower [2]. Two more recent studies with rheumatic disease/autoimmune condition patients provide higher confidence.

[1] ncbi.nlm.nih.gov/pmc/articles/PMC4516647/
[2] academic.oup.com/rheumatology/article/52/1/53/1830871

hospitalization, ↓**25.5%**, p=1.00
COVID-19 case, ↑**49.0%**, p=0.53

Source Study Page Submit Corrections or Comments

5/15 **Positive**

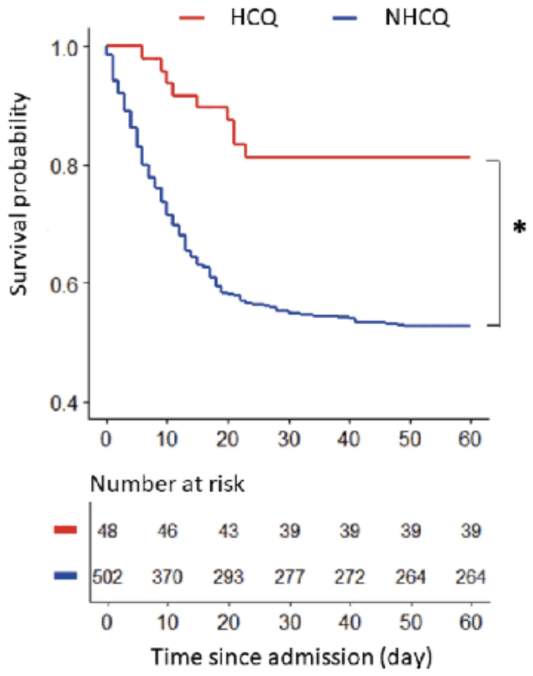
Late treatment study

Yu et al., Science China Life Sciences, 2020 May 15, 1-7, doi:10.1007/s11427-020-1732-2 (Peer Reviewed)

Low Dose of Hydroxychloroquine Reduces Fatality of Critically Ill Patients With COVID-19

Retrospective, 550 critically ill patients. 19% fatality for HCQ versus 47% for non-HCQ, RR 0.395, *p*=0.002.

The levels of inflammatory cytokine IL-6 were significantly reduced from 22.2 pg/mL to 5.2 pg/mL (p<0.05) at the end of the treatment in the HCQ group but there was no change in the control group.



death, ↓60.5%, p=0.002

Source Study Page Submit Corrections or Comments

5/14 **Negative**

Late treatment study

Mahévas et al., BMJ 2020, 369, doi: https://doi.org/10.1136/bmj.m1844 (Peer Reviewed)

Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data

Observational study of 181 patients with advanced disease requiring oxygen showing no benefit for HCQ. Power of study appears too low to support conclusions [1].

None of the 15 patients receiving HCQ+AZ were transferred to intensive care or died compared to 23% overall.

[1] bmj.com/content/369/bmj.m1844/rapid-responses

death, ↑20.0%, p=0.75

Source Study Page Submit Corrections or Comments

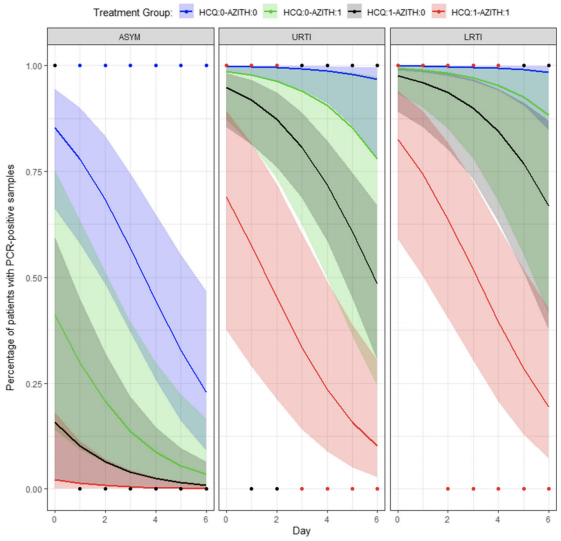
Late treatment study

Okour et al., Journal of Pharmacokinetics and Pharmacodynamics, May 13, 2020, doi:10.1007/s10928-020-09689-x (Peer Reviewed)

Hydroxychloroquine and azithromycin as potential treatments for COVID-19; clinical status impacts the outcome

Odds of PCR-positive decrease by 53% for each unit increase in HCQ log-concentration. Similarly, the odds decrease by 61%, and by 12% for each day increase, and for azithromycin co-treatment, respectively. Computes the minimum HCQ concentration needed based on severity, and corresponding dosage regimens. A loading dose is found to be important. For LRTI and URTI patients the addition of AZ is needed. Extended analysis of Gautret et al. using the observed HCQ concentrations and pharmacokinetic analysis to compute concentrations for all days.

5/13 **Positive**



Source Study Page Submit Corrections or Comments

5/12 **Inconc.**

Pre-Exposure Prophylaxis study

Cassione et al., Annals of the Rheumatic Diseases, doi:10.1136/annrheumdis-2020-217717 (Letter)

COVID-19 infection in a northern-Italian cohort of systemic lupus erythematosus assessed by telemedicine

Survey of 165 SLE patients, 127 on HCQ. 8 patients with suspected COVID-19 and 4 confirmed cases. No mortality, one ICU case. 7 patients had no symptoms despite contact with a COVID-19 patient.

No adjustment for concomitant medications or severity of SLE. Confounding by indication.

COVID-19 case, ↑**49.6%**, p=0.59

Source Study Page Submit Corrections or Comments

5/11 **Inconc.**

Late treatment study

Shabrawishi *et al., medRxix, doi:10.1101/2020.05.08.20095679 (Preprint)*

Negative nasopharyngeal SARS-CoV-2 PCR conversion in response to different therapeutic interventions

Retrospective 93 hospitalized patients in Saudi Arabia showing a non-statistically significant 15% reduction in PCR positive results at day 5, RR 0.85, *p* = 0.65. The treatment group had significantly more severe illness and significantly more male patients.

no virological cure, ↓**14.7%**, p=0.66, risk of no virological cure at day 5

Source Study Page Submit Corrections or Comments

5/11 **Negative**

Late treatment study

Rosenberg *et al., JAMA, May 11, 2020, doi:10.1001/jama.2020.8630 (Peer Reviewed)*

Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Restrospective observational late stage study showing no significant differences but calling for clinical trials.

Zervos et al. [1] point out serious limitations that they say should be corrected on the record: patients receiving HCQ with or without AZ were overall sicker on presentation and had multiple other risk factors including much higher risk based on ethnicity; patients receiving HCQ were more likely to be obese, diabetic, have chronic lung disease, and cardiovascular conditions; yet these sicker patients had approximately the same mortality rates compared to patients with a milder course of the disease and less risk factors. However, the authors conclude that "there are no significant benefits." It is noteworthy that HCQ was associated with a significant survival benefit in a larger cohort of patients from New York City as reported by Mikami et al [2].

[1] ijidonline.com/article/S1201-9712(20)30604-4/fulltext
[2] c19study.com/mikami.html

death, ↑**35.0%**, p=0.31
death, ↑**8.0%**, p=0.79

Source Study Page Submit Corrections or Comments

5/10 **Positive**

Late treatment study

Alberici *et al., Kidney Int., 98:1, 20-26, July 1, 2020, doi:10.1016/j.kint.2020.04.030 (preprint 5/10) (Peer Reviewed)*

A report from the Brescia Renal COVID Task Force on the clinical characteristics and short-term outcome of hemodialysis patients with SARS-CoV-2 infection

Analysis of 94 hemodialysis COVID-19 positive patients. Reduction in death seen with HCQ but *p*=0.12, OR 0.44 [0.16–1.24].

death, ↓**42.9%**, p=0.12
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

5/8 **Ex Vivo**

Ex Vivo

Grassin-Delyle *et al., Clinical Infectious Diseases, doi:10.1093/cid/ciaa546 (Peer Reviewed) (Ex Vivo) (not included in the study count)*

Chloroquine Inhibits the Release of Inflammatory Cytokines by Human Lung Explants

On human lung parenchymal explants, CQ concentration clinically achievable in the lung (100 μM) inhibited the lipopolysaccharide-induced release of TNF-α (by 76%), IL-6 (by 68%), CCL2 (by 72%), and CCL3 (by 67%). In addition to antiviral activity, CQ may also mitigate the cytokine storm associated with severe pneumonia caused by coronaviruses.

Source Study Page Submit Corrections or Comments

5/8 **Positive**

Late treatment study

Carlucci *et al., J. Med. Microbiol., Sep 15, 2020, doi: 10.1099/jmm.0.001250 (preprint 5/8) (Peer Reviewed)*

Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients

Retrospective 932 patients. Addition of Zinc to HCQ+AZ reduces mortality / transfer to hospice, ICU admission, and the need for ventilation.

Reduction in mortality or transfer to hospice adjusted odds ratio OR 0.56, p = 0.002; increase in being discharged home, adjusted OR 1.53, p = 0.008.

Source Study Page Submit Corrections or Comments

5/7 **Inconc.**

Pre-Exposure Prophylaxis study

***Konig** et al., Annals of the Rheumatic Diseases, doi:10.1136/annrheumdis-2020-217690 (Letter)*

Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19

Analysis of 80 SLE patients diagnosed with COVID-19, showing the frequency of hospitalisation did not differ between individuals using an antimalarial versus non-users (55% (16/29) vs 57% (29/51), *p*=ns. Authors suggest that the dosage used may be too low to reach therapeutic levels.

hospitalization, ↓**3.0%**, p=0.88

Source Study Page Submit Corrections or Comments

5/7 **Theory**

Theory

***Derendorf**, H., Int. J. Antimicrobial Agents, 7 May 2020, doi:10.1016/j.ijantimicag.2020.106007 (Peer Reviewed) (Theory) (not included in the study count)*

Excessive lysosomal ion-trapping of hydroxychloroquine and azithromycin

Discusses pharmacokinetic properties of HCQ+AZ as a potential underlying mechanism of the observed antiviral effects.

Source Study Page Submit Corrections or Comments

5/7 **Inconc.**

Late treatment study

***Geleris** et al., NEJM, May 7, 2020, doi:10.1056/NEJMoa2012410 (Peer Reviewed)*

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

There appears to be a major error in this paper. Before propensity matching, 38 control patients had hypertension. After propensity matching, 146 patients had hypertension (Table 1). This is not possible. Even if all propensity matched control patients had hypertension, the control prevalence would only be 14% compared to 49% for treatment. Since patients with hypertension are at much greater risk of mortality (HR 2.12, see [1]), this appears to invalidate the results.

Observational study of 1,446 hospitalized patients showing no significant effect on a combined intubation/death outcome for late treatment.

However, secondary analysis shows the success of HCQ was hidden by combining intubation and death - death / (combined death/intubation) for HCQ was 60% vs. control 89%, for details see: [2].

RCT recommended. No AZ or Zinc. HCQ group much sicker - patients already in mild/moderate ARDS, most of the control group not in ARDS. Control cases received other therapeutics.

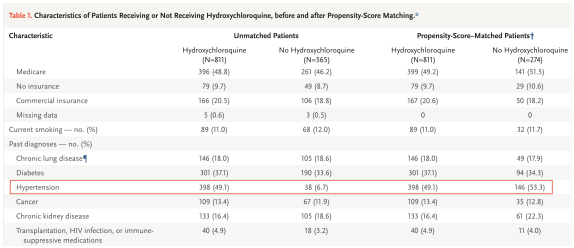


Table 1. Characteristics of Patients Receiving or Not Receiving Hydroxychloroquine, before and after Propensity-Score Matching.[a]

Characteristic	Unmatched Patients		Propensity-Score–Matched Patients[†]	
	Hydroxychloroquine (N=811)	No Hydroxychloroquine (N=565)	Hydroxychloroquine (N=811)	No Hydroxychloroquine (N=274)
Medicare	396 (48.8)	261 (46.2)	399 (49.2)	141 (51.5)
No insurance	79 (9.7)	49 (8.7)	79 (9.7)	29 (10.6)
Commercial insurance	166 (20.5)	106 (18.8)	167 (20.6)	50 (18.2)
Missing data	5 (0.6)	3 (0.5)	0	0
Current smoking — no. (%)	89 (11.0)	68 (12.0)	89 (11.0)	32 (11.7)
Past diagnoses — no. (%)				
Chronic lung disease[¶]	146 (18.0)	105 (18.6)	146 (18.0)	49 (17.9)
Diabetes	301 (37.1)	190 (33.6)	301 (37.1)	94 (34.3)
Hypertension	398 (49.1)	38 (6.7)	398 (49.1)	146 (53.3)
Cancer	109 (13.4)	67 (11.9)	109 (13.4)	35 (12.8)
Chronic kidney disease	133 (16.4)	105 (18.6)	133 (16.4)	61 (22.3)
Transplantation, HIV infection, or immune-suppressive medications	40 (4.9)	18 (3.2)	40 (4.9)	11 (4.0)

[1] academic.oup.com/eurheartj/article/41/22/2058/5851436
[2] twitter.com/dperetti/status/1259154540630364162

combined intubation/death, ↑**4.0%**, p=0.76

Source Study Page Submit Corrections or Comments

5/7 **Positive** (news)

N/A

Sermo *(News) (not included in the study count)*

Sermo reports: COVID-19 treatment trends over 6 weeks and 33,700 interviews: Usage, efficacy and safety perceptions of most-used therapies

HCQ used by 55% of physicians worldwide for COVID. Survey of 6,150 physicians. Currently no formal study is available so this is not included in the study count.

Source Study Page Submit Corrections or Comments

5/6 **Animal**

N/A

Maisonnasse *et al., Nature, 2020, doi:10.1038/s41586-020-2558-4 (preprint 5/6) (Peer Reviewed) (not included in the study count)*

Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates

Monkey study which reports no effect of HCQ or HCQ+AZ. However, there are several signs of effectiveness despite the very small sample sizes and 100% recovery of all

treated and control monkeys.

58% reduction in lung lesions: the final day lung lesion data shows 63% of control monkeys have lesions, while 26% of treated monkeys do, *p*=0.095 (the final day data is missing for 7 monkeys, these are predicted based on the day 5 results and the trend of comparable monkeys).

97% increase in viral load recovery after one week: 3 of 8 control monkeys (38%) have recovered with <= 4 log10 copies/mL viral load, compared to 17 of 23 treated monkeys (74%), *p*=0.095. 3 of 8 (38%) control monkeys also have a higher peak viral load than 100% of the 23 treated monkeys post-treatment. The group with the lowest peak viral load is the PrEP group.

All animals were infected with the same initial viral load, whereas real-world infections vary in the initial viral load, and lower inital viral loads allow greater time to mount an immune response.

Severity of disease is not analyzed as compared to humans. The steep viral drops observed could also be related to immune system response.

Source Study Page Submit Corrections or Comments

5/5 **Positive**

Late treatment study

Membrillo de Novales *et al., Preprints 2020, 2020050057, doi:10.20944/preprints202005.0057.v1 (Preprint)*

Early Hydroxychloroquine Is Associated with an Increase of Survival in COVID-19 Patients: An Observational Study

166 patients hospitalised with COVID-19, HCQ increased survival 1.4 - 1.8 times when patients admitted in early stages. Early is relative to hospital admission here - all patients were in relatively serious condition.

death, **↓55.1%**, p=0.002

Source Study Page Submit Corrections or Comments

5/5 **Positive**

Early, Late

Million *et al., Travel Med Infect Dis., 2020 May 5, doi:10.1016/j.tmaid.2020.101738 (Peer Reviewed)*

Early Treatment of COVID-19 Patients With Hydroxychloroquine and Azithromycin: A Retrospective Analysis of 1061 Cases in Marseille, France

Retrospective 1061 patients. HCQ+AZ safe and results in a low fatality rate.

Source Study Page Submit Corrections or Comments

Pre-Exposure Prophylaxis study

Gendelman *et al., Autoimmunity Reviews, 19:7, July 2020, doi:10.1016/j.autrev.2020.102566 (Peer Reviewed)*

Continuous Hydroxychloroquine or Colchicine Therapy Does Not Prevent Infection With SARS-CoV-2: Insights From a Large Healthcare Database Analysis

Very small study of rheumatic disease/autoimmune disorder patients showing no significant difference but with only 3 chronic HCQ patient cases. Only considers people tested at a time when primarily symptomatic cases were tested.

5/5 **Inconc.**

Other research shows that the risk of COVID-19 for systemic autoimmune disease patients is much higher overall, Ferri et al. show OR 4.42, p<0.001 [1], which is the observed real-world risk, taking into account factors such as these patients potentially being more careful to avoid exposure.

Adjusting for the difference in baseline risk using the result in Ferri et al. shows substantial benefit for HCQ, RR 0.211, but with only 3 HCQ cases the result is inconclusive. More recent studies with rheumatic disease/autoimmune condition patients provide higher confidence.

[1] c19study.com/ferri.html

COVID-19 case, ↓**8.1%**, p=0.88

Source Study Page Submit Corrections or Comments

5/5 **Positive**

Pre-Exposure Prophylaxis study

Mitchell *et al., SSRN, doi:10.2139/ssrn.3586954 (Preprint)*

Markedly Lower Rates of Coronavirus Infection and Fatality in Malaria-Endemic Regions – A Clue As to Treatment?

Analysis of COVID-19 amongst 2.4B people shows a wide counterintuitive disparity between well-developed and less-developed countries, with more affluent countries about one hundred times more likely to be infected and die due to COVID-19. They find the effect is most apparent when comparing to countries with the highest rates of endemic malaria. Since travelers to malaria-endemic countries are likely to be taking antimalarial prophylaxis and there is evidence of efficacy with COVID-19, authors find the data highly probative for the hypothesis that prophylactic antimalarial use by incoming visitors markedly attenuates a country's COVID-19 fatality rate. While authors do not adjust for age differences, those adjustments can only account for a small fraction of the observed difference.

death, ↓**99.0%**, p<0.0001

Source Study Page Submit Corrections or Comments

Pre-Exposure Prophylaxis study

***Huh** et al., medRxiv, doi:10.1101/2020.05.04.20089904 (Preprint)*

Association of previous medications with the risk of COVID-19: a nationwide claims-based study from South Korea

Database analysis of many drugs and COVID-19 cases, with 23 cases taking HCQ, and 251 control patients not taking HCQ, showing OR 1.07, p=0.77, and in multivariable analysis OR 1.48, p=0.086.

Patients taking HCQ are most likely taking it for systemic autoimmune diseases where the risk of COVID-19 is much higher, for example OR 4.42, p<0.001 according to [1] (which includes factors such as systemic autoimmune disease patients potentially being more careful to avoid exposure). The result therefore suggests a substantial benefit for HCQ, as is also shown in Ferri et al. Adjusting for the difference in baseline risk of systemic autoimmune patients results in RR 0.24.

5/4 **Inconc.**

Details of the multivarible analysis in the paper are not provided for assessment, but the analysis may be significantly affected by overfitting and/or multicollinearity. We note that many results in this study differ significantly from other research, for example proton pump inhibitors show OR 0.62, p<0.001 whereas PPIs are classified as "no expected benefit" and other research suggests they increase risk.

[1] c19study.com/ferri.html

COVID-19 case, ↑**47.7%**, p=0.09
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

5/1 **Safety**

N/A

***Mercuro** et al., JAMA Cardiol., May 1, 2020, doi:10.1001/jamacardio.2020.1834 (Peer Reviewed) (not included in the study count)*

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)

Study of 90 hospitalized patients given HCQ, 53 also receiving AZ, 53% hypertension, 29% diabetes mellitus, baseline median QTc 473ms for HCQ, and 442ms for HCQ+AZ. Median change for HCQ+AZ ΔQTc of 23ms vs. 5.5ms for HCQ. Other factors such as stress cardiomyopathy or myocarditis could not be ruled out. Without a control arm, they could not conclude that HCQ and AZ conferred increased cardiotoxic risk; however, compared with HCQ alone, ΔQTc differences were likely associated with the

addition of AZ. The likelihood of prolonged QTc was greater in those who received concomitant loop diuretics or had a baseline QTc of 450 milliseconds or more. HCQ was discontinued in 10 patients due to adverse events including nausea, hypoglycemia, and 1 case of torsades de pointes. There were no deaths reported.

Appropriate use and careful analysis of contraindications, risks, and benefits are important. More recent and much larger studies have not shown significant safety concerns, including outpatient RCTs showing no serious adverse events, and even the RECOVERY trial which used an unusually high dose of HCQ (including 237 patients also receiving AZ) reports they "did not show any excess in ventricular tachycardia (including torsade de pointes) or ventricular fibrillation in the hydroxychloroquine arm", and "serious cardiovascular toxicity has been reported very rarely despite the high prevalence of cardiovascular disease in hospitalized patients, the common occurrence of myocarditis in COVID-19, and the extensive use of hydroxychloroquine and azithromycin together."

Source Study Page Submit Corrections or Comments

5/1 **Safety**

N/A

***Bessière** et al., JAMA Cardiol., May 1, 2020, doi:10.1001/jamacardio.2020.1787 (Peer Reviewed) (not included in the study count)*

Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit

Study of 40 very serious condition ICU patients, 75% required invasive mechanical ventilation, 63% received vasoactive drugs, 50% received other treatments favoring QT prolongation. HCQ with or w/o AZ was given to 45% and 55% respectively. They showed an increase in QTc, more significant with the combination of HCQ+AZ where prolonged QTc was observed in 36% (10 with ΔQTc >60 milliseconds and 7 with QTc ≥500 milliseconds). No ventricular arrhythmia, including torsades de pointes, was recorded. While these results may not be generalizable outside the ICU, caution is recommended in use, especially with the combination.

Appropriate use and careful analysis of contraindications, risks, and benefits are important. More recent and much larger studies have not shown significant safety concerns, including outpatient RCTs showing no serious adverse events, and even the RECOVERY trial which used an unusually high dose of HCQ (including 237 patients also receiving AZ) reports they "did not show any excess in ventricular tachycardia (including torsade de pointes) or ventricular fibrillation in the hydroxychloroquine arm", and "serious cardiovascular toxicity has been reported very rarely despite the high prevalence of cardiovascular disease in hospitalized patients, the common occurrence of myocarditis in COVID-19, and the extensive use of hydroxychloroquine and azithromycin together."

Source Study Page Submit Corrections or Comments

5/2 **Positive** (news)

Late treatment study

Seydi *(News) (not included in the study count)*

Coronavirus: a study in Senegal confirms the effectiveness of hydroxychloroquine

Preliminary results of Senegal trial with 181 patients showing faster recovery with HC Q, and even faster recovery with HCQ+AZ. Currently no formal study is available so this is not included in the study count.

Source Study Page Submit Corrections or Comments

4/30 **Positive**

Early treatment study

Meo *et al., Eur. Rev. Med. Pharmacol. Sci. 2020, 24 (8), 4539-4547, doi:10.26355/eurrev_202004_21038 (Peer Reviewed)*

Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19

Analysis of COVID-19 and malaria, finding that COVID-19 is highly pandemic in countries where malaria is least pandemic, and vice versa, suggesting that CQ/HCQ (widely used for malaria) are protective for COVID-19. This paper also includes a review of 9 articles supporting the efficacy of HCQ and CQ.

Source Study Page Submit Corrections or Comments

4/27 **Positive**

Late treatment study

Sánchez-Álvarez *et al., Nefrología, doi:10.1016/j.nefroe.2020.04.002 (Peer Reviewed)*

Status of SARS-CoV-2 infection in patients on renal replacement therapy. Report of the COVID-19 Registry of the Spanish Society of Nephrology (SEN)

Analysis of 868 patients on renal replacement therapy. Statistically significant reduction in mortality with HCQ for patients on dialysis (OR 0.47, *p*=0.005).

No statistically significant change was found for transplant patients (the result is not given but likely the sample size is too small - the number of transplant patients was half the number of dialysis patients).

death, **↓45.9%**, p=0.005
(odds ratio converted to relative risk)

Source Study Page Submit Corrections or Comments

4/29 **Safety**

		N/A ***Saleh** et al., Circulation: Arrhythmia and Electrophysiology, doi:10.1161/CIRCEP.120.008662 (Peer Reviewed)* The Effect of Chloroquine, Hydroxychloroquine and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection 201 hospitalized patients. No serious side effects of HCQ. No instances of Torsade de pointes, or arrhythmogenic death were reported. They report that although use of these medications resulted in QT prolongation, clinicians seldom need to discontinue therapy. Source Study Page Submit Corrections or Comments
4/25	**In Vitro**	In Vitro ***Andreani** et al., Microbial Pathogenesis, doi:/10.1016/j.micpath.2020.104228 (Peer Reviewed) (In Vitro) (not included in the study count)* In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect HCQ and AZ has a synergistic effect *in vitro* on SARS-CoV-2 at concentrations compatible with that obtained in human lung. Source Study Page Submit Corrections or Comments
4/24	**Inconc.**	Early treatment study ***Ashraf** et al., medRxiv doi:10.1101/2020.04.20.20072421.t (Preprint)* COVID-19 in Iran, a comprehensive investigation from exposure to treatment outcomes Small limited trial with 100 patients concluding that HCQ improved clinical outcome, OR 0.016 [0.002-0.11] in regression analysis. death, **↓67.5%**, p=0.15 Source Study Page Submit Corrections or Comments
4/21	**Positive**	Early treatment study ***Izoulet** M., SSRN, doi:10.2139/ssrn.3575899 (Preprint)*

Countries which Primarily Use Antimalarial Drugs As COVID-19 Treatment See Slower Dynamic of Daily Deaths

Compares the dynamics of daily deaths in the 10 days following the 3rd death in countries using and not using [H]CQ, showing dramatically lower death in [H]CQ countries. This paper does not attempt to account for population age and other differences between the countries and recommends further study.

death, ↓**85.0%**, p<0.001

Source Study Page Submit Corrections or Comments

Late treatment study

Magagnoli *et al., Med (2020), doi:10.1016/j.medj.2020.06.001 (preprint 4/21) (Peer Reviewed)*

Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19

Retrospective 368 hospitalized patients, no statistically significant reduction in mortality or the need for mechanical ventilation with HCQ or HCQ+AZ, or for death with HCQ+AZ, HR 1.83, *p*=0.009 for HCQ mortality.

4/21 **Negative**

The preprint notes that HCQ was more likely to be prescribed to patients with more severe disease, however this was deleted in the published version.

425 patients had dispositions of death or discharge by the end of the study period and thus did not encounter the issue of length-biased sampling and differential rates of right-censored observations among the groups.

death, ↑**31.0%**, p=0.28
death, ↑**83.0%**, p=0.009
death, ↓**11.0%**, p=0.75, HCQ+AZ w/dispositions
death, ↓**1.0%**, p=0.98, HCQ w/dispositions

Source Study Page Submit Corrections or Comments

4/17 **Positive**

Post Exposure Prophylaxis study

Lee *at al., Int. J. Antimicrob. Agents, 2020, Apr 17, doi:10.1016/j.ijantimicag.2020.105988 (Peer Reviewed)*

Can Post-Exposure Prophylaxis for COVID-19 Be Considered as an Outbreak Response Strategy in Long-Term Care Hospitals?

Post exposure prophylaxis of 211 high-risk people after major exposure event in a long term care hospital, showing no positive cases after 14 days.

Source Study Page Submit Corrections or Comments

4/16 **Negative**

Late treatment study

***Borba** et al., JAMA Network Open, doi:10.1001/jamanetworkopen.2020.8857 (Peer Reviewed)*

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)

Comparison of typical CQ dosage with high dosage CQ (600mg CQ twice daily for 10 days), showing higher mortality with high dosage, OR 2.8 [0.9 - 8.5] when controlled by age in multivariate analysis.

Increased incidence of prolonged QT and death in high dose treatment arm. Patients >75 only enrolled in high dose arm, age of high dose arm significantly higher than low dose arm (p=0.02). Very sick at baseline, 43% in ICU, 88.9% on respiratory therapy prior to treatment.

Source Study Page Submit Corrections or Comments

4/15 **Positive**

Early, Late

***Esper** et al., Prevent Senior Institute, São Paulo, Brazil (Preprint)*

Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine

636 patients. HCQ+AZ reduced hospitalization 79% when used within 7 days (65% overall). Non-randomized.

hospitalization, **↓64.0%**, p=0.02

Source Study Page Submit Corrections or Comments

4/15 **Theory**

Theory

***Brufsky**, A., J. Medical Virology, doi:10.1002/jmv.25887 (Peer Reviewed) (Theory) (not included in the study count)*

Hyperglycemia, hydroxychloroquine, and the COVID-19 pandemic

Theory on the effectiveness of HCQ. HCQ has been shown to block the polarization of macrophages to an M1 inflammatory subtype and is predicted to interfere with

glycosylation of a number of proteins involved in the humoral immune response, possibly including the macrophage FcR gamma IgG receptor and other immunomodulatory proteins, potentially through inhibition of UDP-N-acetylglucosamine 2-epimerase. In combination with potential other immunomodulatory effects, this could possibly blunt the progression of COVID-19 pneumonia all to way up to ARDS.

Source Study Page Submit Corrections or Comments

4/14 **Negative**

Late treatment study

***Tang** et al., BMJ 2020, 369, doi:10.1136/bmj.m1849 (Peer Reviewed)*

Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial

150 patients very late stage RCT showing no significant difference. Treatment very late, average 16.6 days after symptom onset.

Data favorable to HCQ was deleted in the second version, see analysis [1].

"[HCQ] accelerate[s] the alleviation of clinical symptoms"

"More rapid alleviation of clinical symptoms with SOC plus HCQ than with SOC alone was observed during the second week since randomization".

"The efficacy of HCQ on the alleviation of symptoms, HR 8.83 [1.09-71.3], was more evident when the confounding effects of other anti-viral agents were removed"

[1] mediterranee-infection.com/tang-et-al-bmj-donnees-favorables-a-lhydroxychloro...

no virological cure, ↓**21.5%**, p=0.51, risk of no virological cure at day 21

Source Study Page Submit Corrections or Comments

4/13 **Review**

Late treatment study

***Gao** et al., Biosci Trends, May 21, 2020, 14:2, 156-158, doi:10.5582/bst.2020.03072, Epub Apr 13, 2020 (Review) (Peer Reviewed) (not included in the study count)*

Update on Use of Chloroquine/Hydroxychloroquine to Treat Coronavirus Disease 2019 (COVID-19)

Increasing evidence from completed clinical studies shows CQ and HCQ effective (HCQ more effective).

Source Study Page Submit Corrections or Comments

4/12	**Negative**	Late treatment study *Barbosa et al., Preprint (Preprint)* Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomized comparative study Small retrospective study with 63 patients (32 treated with HCQ), showing no effectiveness, however the baseline state of each arm significantly differs. This preprint was submitted to NEJM but has not been published several months later. death, ↑147.0%, p=0.58 Source Study Page Submit Corrections or Comments
4/11	**Positive**	Early treatment study *Gautret et al., Travel Medicine and Infectious Disease, doi:10.1016/j.tmaid.2020.101663 (Peer Reviewed)* Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study Pilot study suggesting improvement with HCQ+AZ and recommending further study. 80 patients with relatively mild cases, no control group, and no attempt to analyze confounding factors. Source Study Page Submit Corrections or Comments
4/10	**Meta**	Late treatment study *Lover, medRxiv, doi:10.1101/2020.03.22.20040949 (Preprint) (meta analysis - not included in study count)* Quantifying treatment effects of hydroxychloroquine and azithromycin for COVID-19: a secondary analysis of an open label non-randomized clinical trial (Gautret et al, 2020) Secondary analysis of Gautret et al. showing "modest to no impact of HCQ treatment, with more significant effects from [HCQ+AZ]". Source Study Page Submit Corrections or Comments
4/3	**Theory**	

		Theory *Fantini et al., Int J Antimicrob Agents, 55:5, doi:10.1016/j.ijantimicag.2020.105960 (Peer Reviewed) (Theory) (not included in the study count)* Structural and molecular modelling studies reveal a new mechanism of action of ch loroquine and hydroxychloroquine against SARS-CoV-2 infection In-silico analysis confirming the antiviral properties of CQ, showing a new mechanism of action of CQ, and showing that HCQ is more potent than CQ. Source Study Page Submit Corrections or Comments
4/1	**Positive**	Early treatment study *Huang et al., Journal of Molecular Cell Biology, Volume 12, Issue 4, April 2020, 322–325, doi:10.1093/jmcb/mjaa014 (Peer Reviewed)* Treating COVID-19 with Chloroquine 22 patients. All CQ patients discharged by day 14 versus 50% of Lopinavir/Rotinavir patients. Symptom onset to treatment 2.5 days for CQ vs. 6.5 days for Lopinavir/Rotinavir. no recovery, ↓**90.9%**, p=0.09, risk of no recovery at day 14 no improvement in pneumonia, ↓**83.0%**, p=0.22, risk of no improvement in pneumonia at day 14 Source Study Page Submit Corrections or Comments
3/31	**Positive**	Late treatment study *Chen et al., medRxiv doi:10.1101/2020.03.22.20040758 (Preprint)* Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial 62 patients. RCT showing significantly faster recovery with HCQ. 13% progressed to severe cases in the control group, versus 0% for the treatment group. Significant improvement seen in pneumonia on chest CT for 61% of treated patients and 16% of control patients. no improvement in pneumonia, ↓**57.0%**, p=0.04, risk of no improvement in pneumonia at day 6 Source Study Page Submit Corrections or Comments
3/31	**In Vitro**	

		In Vitro ***Clementi*** *et al., Front. Microbiol., 10 July 2020, doi:10.3389/fmicb.2020.01704 (preprint 3/31) (Peer Reviewed) (In Vitro) (not included in the study count)* Combined Prophylactic and Therapeutic Use Maximizes Hydroxychloroquine Anti-SARS-CoV-2 Effects in vitro *In vitro* study, not included in the study count or percentages, showing greater inhibition for combined pre and post-exposure treatment for Vero E6 and Caco-2 cells. Source Study Page Submit Corrections or Comments
3/28	**Negative**	Late treatment study ***Molina*** *et al., Médecine et Maladies Infectieuses, 50:4, June 2020, 10.1016/j.medmal.2020.03.006 (preprint 3/28) (Letter)* No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection 11 patients with severe cases. No evidence of benefit for HCQ. Binary PCR evaluation with an unknown Ct. Source Study Page Submit Corrections or Comments
3/26	**Positive**	Late treatment study ***Zhong*** *Nanshan (钟南山) (Preprint)* Efficacy and safety of chloroquine for treatment of COVID-19. An open-label, multi-center, non-randomized trial 197 patients. CQ effective. Day 10 viral RNA negative 91.4% HCQ versus 57.4% control. Median time to negative test 3 days versus 9 days for control. no virological cure, **↓80.0%**, p<0.0001, risk of no virological cure at day 10 Source Study Page Submit Corrections or Comments
3/24	**Theory**	Theory ***Pagliano*** *et al., Clin. Infect. Dis., 2020 Mar 24, doi:10.1093/cid/ciaa320 (Peer Reviewed) (Theory) (not included in the study count)*

Is Hydroxychloroquine a Possible Post-Exposure Prophylaxis Drug to Limit the Transmission to Health Care Workers Exposed to COVID19?

CQ and HCQ inhibit replication at early stages of infection, no similar effect reported for other drugs which are only able to interfere after cell infection. Large volume of existing data on safety. (8/23: we corrected the classification of this study)

Source Study Page Submit Corrections or Comments

Theory

Hu et al., Nature Nanotechnology, 15, 247–249, 2020, doi:10.1038/s41565-020-0674-9 (Peer Reviewed) (Theory) (not included in the study count)

3/23 **Theory**

Insights from nanomedicine into chloroquine efficacy against COVID-19

CQ is known in nanomedicine research for the investigation of nanoparticle uptake in cells, and may have potential for the treatment of COVID-19.

Source Study Page Submit Corrections or Comments

Pre-Exposure Prophylaxis study

ICMR, Indian Council of Medical Research (Advisory) (not included in the study count)

3/21 **Positive** (advisory)

Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection

Recommends HCQ for prophylaxis in asymptomatic healthcare workers as found effective in-vitro and in-vivo. Currently no formal study is available so this is not included in the study count.

Source Study Page Submit Corrections or Comments

Late treatment study

Hu et al., Shanghai Combined Task Force on COVID-19 (News) (not included in the study count)

3/20 **Positive** (news)

Shanghai Experience of COVID-19 Management

Clinical studies of HCQ with 184 cases and 21 hospitals show HCQ is effective. Currently no formal study is available so this is not included in the study count.

Source Study Page Submit Corrections or Comments

3/18 **In Vitro**

In Vitro

Liu et al., Cell Discovery 6, 16 (2020), doi:10.1038/s41421-020-0156-0 (Peer Reviewed) (In Vitro) (not included in the study count)

Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro

HCQ effective *in vitro* and less toxic than CQ. In addition to direct antiviral activity, HC Q is a safe and successful anti-inflammatory agent that has been used extensively in autoimmune diseases and can significantly decrease the production of cytokines and, in particular, pro-inflammatory factors. Therefore, in COVID-19 patients, HCQ may also contribute to attenuating the inflammatory response. Careful design of clinical trials is important to achieve efficient and safe control of the infection.

Source Study Page Submit Corrections or Comments

3/17 **Inconc.**

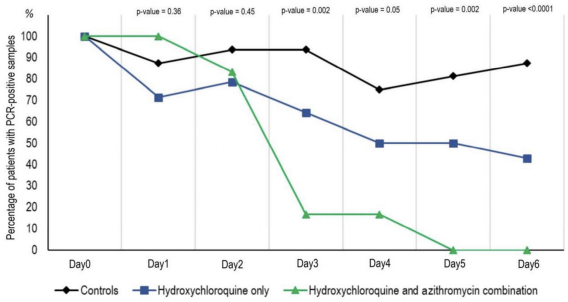
Early treatment study

***Gautret** et al., Int. J. of Antimicrobial Agents, 17 March 2020, doi:10.1016/j.ijantimicag.2020.105949 (Peer Reviewed)*

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an openlabel non-randomized clinical trial

HCQ was significantly associated with reduction / elimination of viral load, which was enhanced with AZ. Updated 8/13: responses to this paper have raised methodological issues [1, 2, 3].

Despite the limitations, this early observational study was a milestone in the discovery process, including detailed daily evolution of PCR positivity. This study should be viewed in the context of the series of studies from this group.



[1] sciencedirect.com/science/article/pii/S092485792030251X
[2] sciencedirect.com/science/article/pii/S0924857920302338
[3] sciencedirect.com/science/article/pii/S0924857920302260

no virological cure, ↓**66.0%**, p=0.001, risk of no virological cure at day 6

Source Study Page Submit Corrections or Comments

3/17 **Review**

N/A

Sahraei *et al., Int. J. Antimicrobial Agents, April 2020, 55:4, doi:10.1016/j.ijantimicag.2020.105945 (Review) (Peer Reviewed) (not included in the study count)*

Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine

Discussion of mechanisms of action, CQ vs. HCQ, early studies, safety.

Source Study Page Submit Corrections or Comments

3/13 **Review**

N/A

Todaro *and Rigano (Review) (Preprint) (not included in the study count)*

An Effective Treatment for Coronavirus (COVID-19)

Discussion of existing research, treatment guidelines, and mechanisms of action for CQ and HCQ, recommending use.

Source Study Page Submit Corrections or Comments

3/12 **Theory**

Theory

Devaux *et al., International Journal of Antimicrobial Agents, doi:10.1016/j.ijantimicag.2020.105938 (Peer Reviewed) (Theory) (not included in the study count)*

New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19?

Discusses mechanisms of CQ interference with the SARS-CoV-2 replication cycle.

Source Study Page Submit Corrections or Comments

3/10 **Meta**

N/A

Cortegiani *et al., J. Crit. Care, June 2020, 57:279-283, doi:10.1016/j.jcrc.2020.03.005, Epub Mar 10, 2020 (Peer Reviewed) (meta analysis - not included in study count)*

A Systematic Review on the Efficacy and Safety of Chloroquine for the Treatment of COVID-19

Review of six articles and 23 ongoing clinical trials in China recommending research and clinical use adhering to MEURI.

Source Study Page Submit Corrections or Comments

N/A

Yao et al., Clin. Infect. Dis., 2020 Mar 9, doi:10.1093/cid/ciaa237 (Peer Reviewed) (not included in the study count)

3/9 **In Vitro**

In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

HCQ is more potent than CQ *in vitro* for inhibiting SARS-CoV-2. Simulates HCQ concentration in lung fluid and provides dosing recommendations.

Source Study Page Submit Corrections or Comments

3/6 **Negative**

Late treatment study

Chen et al., J. Zhejiang University (Med Sci), doi:10.3785/j.issn.1008-9292.2020.03.03 (Peer Reviewed)

A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)

30 moderate hospitalized cases, all recovered. Time to RNA negative comparable. Less frequent radiological progression with HCQ but not statistically significant. One HCQ patient developed to a severe case. Treatment group 4 years older and with higher incidence of hypertension.

组　别	*n*	男　性*	平均年龄（岁）
试验组	15	9(60.0)	50.5±3.8
对照组	15	12(80.0)	46.7±3.6
t/*U* 值	—	—	0.72
P 值	—	>0.05	>0.05

disease progression, ↓29.0%, p=0.57, risk of radiological progression
no virological cure, ↑100%, p=1.00, risk of viral+ at day 7

Source Study Page Submit Corrections or Comments

3/4 **Review**

Late treatment study

Colson *et al., Int J. Antimicrob Agents, doi: 10.1016/j.ijantimicag.2020.105932. Epub 2020 Mar 4. (Review) (Peer Reviewed) (not included in the study count)*

Chloroquine and Hydroxychloroquine as Available Weapons to Fight COVID-19

Recommending CQ and HCQ for COVID-19 based on 20 clinical studies in China and a strong rationale for use.

Source Study Page Submit Corrections or Comments

2/20 **Positive**

Late treatment study

Jiang *et al., Chin. J. Tuberc. Respir. Dis., 2020, 43, doi:10.3760/cma.j.issn.1001-0939.2020.0019 (Peer Reviewed)*

Expert Consensus on Chloroquine Phosphate for the Treatment of Novel Coronavirus Pneumonia

Early trials in China show CQ results in shorter hospital stays and improved patient outcomes.

Source Study Page Submit Corrections or Comments

2/19 **Positive**

Late treatment study

Gao *et al., BioScience Trends, 2020, doi:10.5582/bst.2020.01047 (Peer Reviewed)*

Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies

Results from 15 clinical trials in China showing CQ is effective.

Source Study Page Submit Corrections or Comments

2/17 **Positive** (news)

Late treatment study

Sun *Yanrong, deputy head of the China National Center for Biotechnology Development*

(News) (not included in the study count)

Antimalarial drug confirmed effective on COVID-19

HCQ under clinical trials in >10 hospitals in China and has shown fairly good efficacy. Currently no formal study is available so this is not included in the study count.

Source Study Page Submit Corrections or Comments

Late treatment study

***Xia** et al., ChiCTR2000029741 (Preprint)*

Efficacy of Chloroquine and Lopinavir/ Ritonavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter randomized controlled clinical study

2/11 **Positive**

Early results from a very small trial, reported within the application for a later trial. Very minimal details are provided, but we include this as the earliest published results. For COVID-19 patients with pneumonia the viral negative conversion rate was 50% (5/10) with CQ versus 20% (3/15) with lopinavir/ritonavir.

no virological cure, ↓**37.5%**, p=0.17

Source Study Page Submit Corrections or Comments

In Vitro

***Wang** et al., Cell Res. 30, 269–271, doi:L10.1038/s41422-020-0282-0 (Peer Reviewed) (In Vitro) (not included in the study count)*

2/4 **In Vitro**

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

In vitro study, not included in the study count or percentages. Remdesivir and CQ potently blocked virus infection *in vitro*.

Source Study Page Submit Corrections or Comments

2017 **Dosing**

N/A

***Chhonker** et al., Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences, 22 Nov 2017, 1072:320-327 doi:10.1016/j.jchromb.2017.11.026 (Peer Reviewed) (not included in the study count)*

Simultaneous quantitation of hydroxychloroquine and its metabolites in mouse blood

and tissues using LC-ESI-MS/MS: An application for pharmacokinetic studies

Presents a method for quantification of HCQ in mouse blood and tissues. They show a lung concentration significantly higher than other organs, and about 30 times the blood concentration.

Source Study Page Submit Corrections or Comments

2014 **Animal**

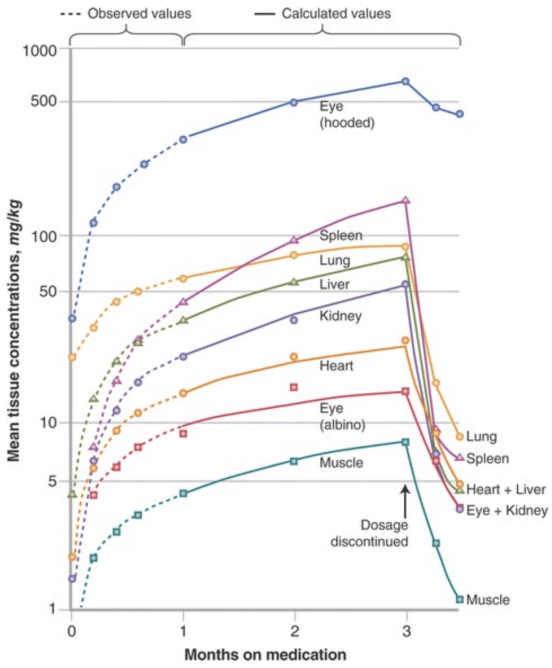
Animal study

***Browning**, D., Pharmacology of Chloroquine and Hydroxychloroquine, 2014, 35-63, doi:10.1007/978-1-4939-0597-3_2 (Peer Reviewed) (not included in the study count)*

Pharmacology of Chloroquine and Hydroxychloroquine

Review of the pharmacology of CQ and HCQ. Some notable points:

- HCQ and CQ are equipotent but CQ is more toxic, the therapeutic ratio is higher for HCQ.
- Concentrations in different tissues can vary >10x, in particular the concentration in the lung is much higher in animal experiments.
- Tissue uptake as a function of dosage is nonlinear.



Source Study Page Submit Corrections or Comments

2014 **In Vitro**

In Vitro

		de Wilde et al., Antimicrobial Agents and Chemotherapy, Jul 2014, 58:8, 4875-4884, doi:10.1128/AAC.03011-14 (Peer Reviewed) (In Vitro) (not included in the study count) Screening of an FDA-Approved Compound Library Identifies Four Small-Molecule Inhibitors of Middle East Respiratory Syndrome Coronavirus Replication in Cell Culture CQ inhibits SARS-CoV, MERS-CoV, and HCoV-229E-GFP replication in the low-micromolar range. Source Study Page Submit Corrections or Comments
2012	**Animal**	Animal study *Yan et al., Cell Research, 23, 300–302, doi:10.1038/cr.2012.165 (Peer Reviewed) (not included in the study count)* Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model CQ, a known autophagy inhibitor that is in clinical use, can efficiently ameliorate acute lung injury and dramatically improve the survival rate in mice infected with live avian influenza A H5N1 virus. Source Study Page Submit Corrections or Comments
2009	**Animal**	Animal study *Keyaerts et al., Antimicrob. Agents Chemother, August 2009, 53(8), doi:0.1128/AAC.01509-08 (Peer Reviewed) (not included in the study count)* Antiviral Activity of Chloroquine against Human Coronavirus OC43 Infection in Newborn Mice CQ inhibits HCoV-OC43 replication in HRT-18 cells. A lethal HCoV-OC43 infection in newborn C57BL/6 mice can be treated with CQ acquired transplacentally or via maternal milk. The highest survival rate (98.6%) was found when mother mice were treated daily with a concentration of 15 mg of CQ per kg of body weight. Survival rates declined in a dose-dependent manner, with 88% survival when treated with 5 mg/kg CQ and 13% survival when treated with 1 mg/kg CQ. CQ can be highly effective against HCoV-OC43 infection in newborn mice and may be considered as a future drug against HCoVs. Source Study Page Submit Corrections or Comments
2008	**In Vitro**	In Vitro

Kono et al., Antiviral Research, 77:2, February 2008, 150-152, 10.1016/j.antiviral.2007.10.011 (Peer Reviewed) (In Vitro) (not included in the study count)

Inhibition of human coronavirus 229E infection in human epithelial lung cells (L132) by chloroquine: Involvement of p38 MAPK and ERK

CQ significantly decreased viral replication of HCoV-229E at concentrations lower than in clinical usage. CQ affects the activation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK). p38 MAPK inhibitor, SB203580, inhibits CPE induced by HCoV-229E infection and viral replication.

Source Study Page Submit Corrections or Comments

2006 **In Vitro**

In Vitro

Savarino et al., Lancet Infect. Dis., doi:10.1016/S1473-3099(06)70361-9 (Peer Reviewed) (In Vitro) (not included in the study count)

New insights into the antiviral effects of chloroquine

Update to 2003 paper, not included in the study count or percentages. Hypothesis of CQ inhibiting SARS replication has been confirmed in two in-vitro studies. CQ affected an early stage of SARS replication.

Source Study Page Submit Corrections or Comments

2005 **In Vitro**

In Vitro

Vincent et al., Virol. J. 2:69, 2005, doi:10.1186/1743-422X-2-69 (Peer Reviewed) (In Vitro) (not included in the study count)

Chloroquine is a potent inhibitor of SARS coronavirus infection and spread

In vitro study, SARS-CoV-1, not included in the study count or percentages. CQ has strong antiviral effects on SARS CoV infection when cells treated either before or after exposure, suggesting prophylactic and treatment use. Describes three mechanisms by which the drug might work and suggests it may have both a prophylactic and therapeutic role in coronavirus infections.

Source Study Page Submit Corrections or Comments

2004 **In Vitro**

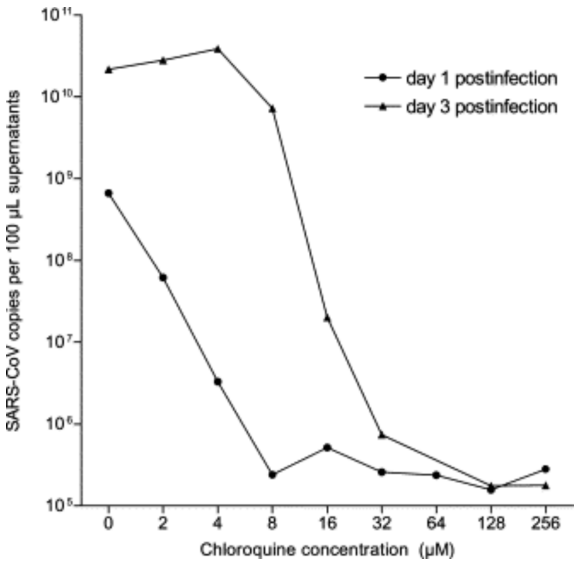
In Vitro

Keyaerts et al., Biochem. Biophys. Res. Comm., 323:1, 8 October 2004,

doi:10.1016/j.bbrc.2004.08.085 (Peer Reviewed) (In Vitro) (not included in the study count)

In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine

In vitro study, SARS-CoV-1, not included in the study count or percentages. IC50 of CQ for antiviral activity (8.8) is significantly lower than cytostatic activity CC50 (261.3), selectivity index of 30. IC50 for inhibition of SARS-CoV *in vitro* approximates the plasma concentrations of CQ reached during treatment of acute malaria. CQ may be considered for immediate use in the prevention and treatment of SARS-CoV infections.



Source Study Page Submit Corrections or Comments

Theory

Savarino et al., Lancet Infect. Dis., doi:10.1016/S1473-3099(03)00806-5 (Peer Reviewed) (Theory) (not included in the study count)

Effects of chloroquine on viral infections: an old drug against today's diseases

2003 **Theory**

Not included in the study count or percentages. Discussion/review noting that CQ exerts antiviral effects, inhibiting the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. Notes that CQ has immunomodulatory effects, suppressing the production/release of tumour necrosis factor α and interleukin 6, which mediate the inflammatory complications of several viral diseases.

Source Study Page Submit Corrections or Comments

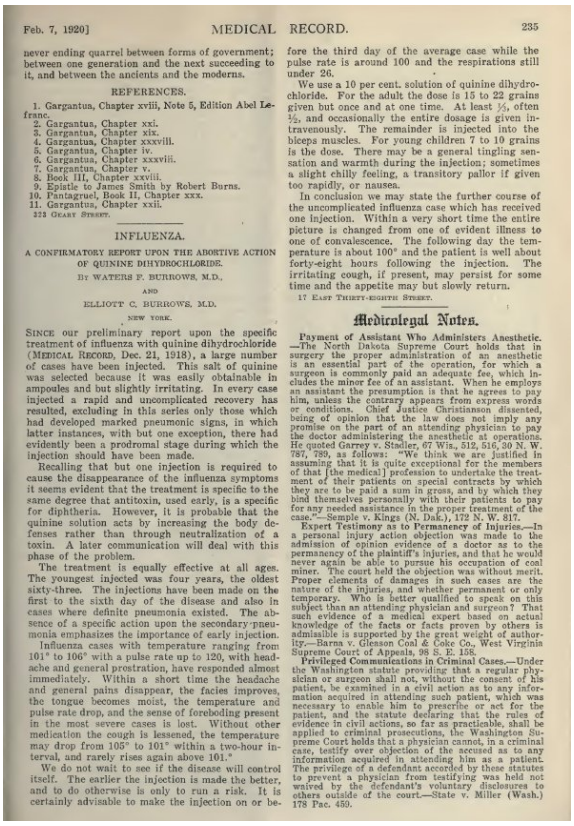
1918 **Inconc.**

N/A

***Burrows**, E., Medical Record, 97:6, 235, Feb 7, 1920 (Peer Reviewed) (not included in the study count)*

A confirmatory report upon the abortive action of quinine dihydrochloride

Quinine was found to be effective for the Spanish Flu in 1918.



Feb. 7, 1920] MEDICAL RECORD. 235

never ending quarrel between forms of government; between one generation and the next succeeding to it, and between the ancients and the moderns.

REFERENCES.

1. Gargantua, Chapter xviii, Note 5, Edition Abel Lefranc.
2. Gargantua, Chapter xxi.
3. Gargantua, Chapter xix.
4. Gargantua, Chapter xxxviii.
5. Gargantua, Chapter iv.
6. Gargantua, Chapter xxxviii.
7. Gargantua, Chapter v.
8. Book III, Chapter xxviii.
9. Epistle to James Smith by Robert Burns.
10. Pantagruel, Book II, Chapter xxx.
11. Gargantua, Chapter xxii.

223 Geary Street.

INFLUENZA.

A CONFIRMATORY REPORT UPON THE ABORTIVE ACTION OF QUININE DIHYDROCHLORIDE.

By Waters P. Burrows, M.D.

AND

Elliott C. Burrows, M.D.

New York.

Since our preliminary report upon the specific treatment of influenza with quinine dihydrochloride (Medical Record, Dec. 21, 1918), a large number of cases have been injected. This salt of quinine was selected because it was easily obtainable in ampoules and but slightly irritating. In every case injected a rapid and uncomplicated recovery has resulted, excluding in this series only those which had developed marked pneumonic signs, in which latter instances, with but one exception, there had evidently been a prodromal stage during which the injection should have been made.

Recalling that but one injection is required to cause the disappearance of the influenza symptoms it seems evident that the treatment is specific to the same degree that antitoxin, used early, is a specific for diphtheria. However, it is probable that the quinine solution acts by increasing the body defenses rather than through neutralization of a toxin. A later communication will deal with this phase of the problem.

The treatment is equally effective at all ages. The youngest injected was four years, the oldest sixty-three. The injections have been made on the first to the sixth day of the disease and also in cases where definite pneumonia existed. The absence of a specific action upon the secondary pneumonia emphasizes the importance of early injection.

Influenza cases with temperature ranging from 101° to 106° with a pulse rate up to 120, with headache and general prostration, have responded almost immediately. Within a short time the headache and general pains disappear, the facies improves, the tongue becomes moist, the temperature and pulse rate drop, and the sense of foreboding present in the most severe cases is lost. Without other medication the cough is lessened, the temperature may drop from 105° to 101° within a two-hour interval, and rarely rises again above 101.°

We do not wait to see if the disease will control itself. The earlier the injection is made the better, and to do otherwise is only to run a risk. It is certainly advisable to make the injection on or before the third day of the average case while the pulse rate is around 100 and the respirations still under 26.

We use a 10 per cent. solution of quinine dihydrochloride. For the adult the dose is 15 to 22 grains given but once and at one time. At least ½, often ½, and occasionally the entire dosage is given intravenously. The remainder is injected into the biceps muscles. For young children 7 to 10 grains is the dose. There may be a general tingling sensation and warmth during the injection; sometimes a slight chilly feeling, a transitory pallor if given too rapidly, or nausea.

In conclusion we may state the further course of the uncomplicated influenza case which has received one injection. Within a very short time the entire picture is changed from one of evident illness to one of convalescence. The following day the temperature is about 100° and the patient is well about forty-eight hours following the injection. The irritating cough, if present, may persist for some time and the appetite may but slowly return.

17 East Thirty-eighth Street.

Medicolegal Notes.

Payment of Assistant Who Administers Anesthetic.—The North Dakota Supreme Court holds that in surgery the proper administration of an anesthetic is an essential part of the operation, for which a surgeon is commonly paid an adequate fee, which includes the minor fee of an assistant. When he employs an assistant the presumption is that he agrees to pay him, unless the contrary appears from express words or conditions. Chief Justice Christianson dissented, being of opinion that the law does not imply any promise on the part of an attending physician to pay the doctor administering the anesthetic at operations. He quoted Garvey v. Stadler, 67 Wis., 512, 516, 30 N. W. 787, 789, as follows: "We think we are justified in assuming that it is quite exceptional for the members of that [the medical] profession to undertake the treatment of their patients on special contracts by which they are to be paid a sum in gross, and by which they bind themselves personally with their patients to pay for any needed assistance in the proper treatment of the case."—Semple v. Kings (N. Dak.), 172 N. W. 817.

Expert Testimony as to Permanency of Injuries.—In a personal injury action objection was made to the admission of opinion evidence of a doctor as to the permanency of the plaintiff's injuries, and that he would never again be able to pursue his occupation of coal miner. The court held the objection was without merit. Proper elements of damages in such cases are the nature of the injuries, and whether permanent or only temporary. Who is better qualified to speak on this subject than an attending physician and surgeon? That such evidence of a medical expert based on actual knowledge of the facts or facts proven by others is admissible is supported by the great weight of authority.—Barna v. Gleason Coal & Coke Co., West Virginia Supreme Court of Appeals, 98 S. E. 158.

Privileged Communications in Criminal Cases.—Under the Washington statute providing that a regular physician or surgeon shall not, without the consent of his patient, be examined in a civil action as to any information acquired in attending such patient, which was necessary to enable him to prescribe or act for the patient, and the statute declaring that the rules of evidence in civil actions, so far as practicable, shall be applied to criminal prosecutions, the Washington Supreme Court holds that a physician cannot, in a criminal case, testify over objection of the accused as to any information acquired in attending him as a patient. The privilege of a defendant accorded by these statutes to prevent a physician from testifying was held not waived by the defendant's voluntary disclosures to others outside of the court.—State v. Miller (Wash.) 178 Pac. 450.

Source Study Page Submit Corrections or Comments

1890 **Inconc.** (news)

N/A

***Le Grelot** (News) (not included in the study count)*

Quinine use for the Russian influenza pandemic if 1889-1890

Quinine and antipyrine, a bitherapy for defying death during the Russian influenza pandemic of 1889-1890 (around 40,000 deaths in France at the beginning of 1890). Currently no formal study is available so this is not included in the study count.

20e ANNÉE — N° 979. FRANCE : 15 CENTIMES 12 Janvier 1890

LE GRELOT

BUREAUX
5, cité Bergère, 5
PARIS

ABONNEMENTS
FRANCE
Un an. . . . . 8 fr. »
Six mois . . . 4 »
Trois mois . . 2 »
15 c. le numéro

PARAIT LE DIMANCHE

ADRESSER
Lettres & Mandats à M. J. MADRE
Directeur-Gérant

BUREAUX
5, cité Bergère, 5
PARIS

ABONNEMENTS
ÉTRANGER
Un an. . . . . 10 fr. »
Six mois . . . 5 »
Trois mois . . 2 50
20 c. le numéro

PARAIT LE DIMANCHE

PUBLICITÉ
Les annonces sont reçues aux bureaux du journal

Tout abonné à un journal de Paris peut recevoir gratuitement le GRELOT (Voir en tête de la 2e page)

TOUT LE MONDE L'A (ter) L'INFLUENZA!

La Ronde des Médecins et des Potards.

Source Study Page Submit Corrections or Comments

1889 **Inconc.** (news)

N/A

Edwin Wiley Grove (News) (not included in the study count)

Laxative Bromo Quinine

Quinine has been used for respiratory infections since 1889. Not included in the study count or percentages, just as an interesting observation.