

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020;383:517-25. DOI: 10.1056/NEJMoa2016638

(PDF last updated December 4, 2020)

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Methods S1. Additional Exclusion Criteria

Additional relatively rare exclusion criteria included: those having a hydroxychloroquine allergy, retinal eye disease, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, chronic kidney disease (stage 4 or 5 or receiving dialysis), porphyria, weight less than 40 kg, receiving chemotherapy, or concurrently using hydroxychloroquine, azithromycin or cardiac arrhythmia medications.

In Canada, additional exclusions consisted of pregnancy, breastfeeding, severe diarrhea or vomiting, known cirrhosis with encephalopathy or ascites, known prolonged cardiac QT interval, ventricular arrhythmia, or history of sudden cardiac death, or QT-prolonging medicines.¹

On April 20, 2020, the US Food and Drug Administration (FDA) required additional exclusions of structural or ischemic heart disease, personal or family history of cardiac QT prolongation, or QT-prolonging medications, and weight less than 50kg

Concomitant medication exclusion criteria included current use of:

- hydroxychloroquine, chloroquine
- Cardiac medicines of: flecainide; amiodarone; digoxin; procainamide; or sotalol.
- QT prolonging medicines of:
 - Antimicrobials: azithromycin clarithromycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, ketoconazole, itraconazole, or mefloquine
 - Antidepressants: amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, wellbutrin, or venlafaxine
 - Antipsychotic or mood stabilizers: haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone
 - Methadone
 - Sumatriptan, zolmitriptan

Methods S2. Clinical Case Definition

*U.S. Council of State and Territorial Epidemiologists Covid-19 Case Criteria, as defined on April 5, 2020 (Interim-20-ID-01).*²

Clinical Criteria for Reporting¹

In outpatient or telehealth settings at least two of the following symptoms:

- fever (measured or subjective),
- chills,
- rigors,
- myalgia,
- headache,
- sore throat,
- new olfactory and/or taste disorder(s)

OR

at least one of the following symptoms:

- cough,
- shortness of breath, or
- difficulty breathing

OR

Severe respiratory illness with at least one of the following:

- Clinical or radiographic evidence of pneumonia, or
- Acute respiratory distress syndrome (ARDS).

AND

No alternative more likely diagnosis

Use in this Trial: The above case definition assumes no epidemiologic linkage. All trial participants had epidemiologic linkage. Participants meeting the above case definition are classified as “Probable” Covid-19 cases.

Epidemiological Linkage Criteria for Reporting

Clinically compatible symptoms with one or more of the following exposures in the 14 days before onset of symptoms:

- Close contact** with a person diagnosed with COVID-19;
- Travel to or residence in an area with sustained, ongoing community transmission of SARS-CoV-2;
- Member of a risk cohort as defined by public health authorities during an outbreak.

** Close contact with a person diagnosed with COVID-19; whereby close contact is defined as being within 6 feet for a period of 10 minutes to 30 minutes or more depending upon the exposure. In healthcare settings, this may be defined as exposures of greater than a few minutes or more. Data are insufficient to precisely define the duration of exposure that constitutes prolonged exposure and thus a close contact.

Participants who had 1 compatible symptom of their illness with the epidemiologic linkage were classified as “Possible” Covid-19 cases for purposes of our trial. Per the Council of State and

Territorial Epidemiologists reporting guidelines, these are also reported as Probable Cases; however, we use “Possible” herein to distinguish from the more robust symptom complex of Probable Cases. Notably diarrhea is not a symptom used in the U.S. case definition.

Definitions of PPE and risk

All enrolled persons reported household or occupational contact for <6 feet for >10 minutes, and levels of risk were defined as:

High risk = no eye shield, no facemask, and no respirator

Moderate risk = no eye shield; however, a simple surgical facemask or respirator was used.

Low risk persons wearing eye shield and facemask or respirator were not enrolled into the trial
Persons with contact of <10 minutes or >6 feet distance were not enrolled into the trial.

Table S1. Participant Status at Time of Trial Completion

Status	Hydroxychloroquine (n=414)	Placebo (n=407)
Completed day 14	364 (87.9%)	361 (88.7%)
Lost to follow-up	46 (11.1%)	42 (10.3%)
Withdrawal of consent	4 (1.0%)	4 (1.0%)
Death	0 (0%)	0 (0%)
Among those Lost to Follow Up*		
Some survey data, vital status after day 14 known	8 (1.9%)	8 (2.0%)
No survey data, vital status after day 14 known	2 (0.5%)	1 (0.2%)
Some survey data, vital status after day 14 unknown	13 (3.1%)	4 (1.0%)
No survey data, vital status after day 14 unknown	23 (5.6%)	29 (7.1%)
Overall Lost to Follow Up	46 (11.1%)	42 (10.3%)

*The *a priori* assumption in designing this internet-based trial was a 20% lost to follow up. For those not responding to email surveys, co-investigators emailed, texted, and called participants and/or their next-of-kin to attempt to assess vital status.

Sensitivity analyses:

1) When participants are removed from the analyses who have NO survey data (ie, denominator is smaller), the results are:

- Hydroxychloroquine 49/389 = 12.6% versus Placebo 58/377 = 15.4%; p=0.30

2) When it is assumed that those who have no survey data ARE EVENTS (i.e., numerators larger), the results are:

- Hydroxychloroquine 74/414 = 17.9% versus Placebo 88/407 = 21.6%; p=0.19

3) When it is assumed that all those missing day 14 survey data are events (i.e. even larger numerators), the results are:

- Hydroxychloroquine 91/414 = 22% versus Placebo 98/407 = 24.1%; p=0.51

Table S2. Assignment to Clinical Case Definition

Of 117 persons with new reported symptoms and/or testing, the distribution was:

Asymptomatic PCR+ (n=1). Three additional persons who later became symptomatic with anosmia (n=2) and fatigue (n=1) as included below.

Distribution of Symptoms n=115 Symptomatic; 18 PCR+

We utilized the U.S. Council for State and Territorial Epidemiologists Covid-19 Case Criteria, as defined on April 5, 2020 (Interim-20-ID-01) as the basis for defining case definitions, with infectious diseases adjudication thereafter.² All adjudication was blinded without knowledge of the randomization assignment or later PCR results.

<https://www.cdc.gov/coronavirus/2019-ncov/covid-data/faq-surveillance.html>

Adjudicated Clinical Case Classification*

Final Classification	Adjudicated Clinical Case Classification*				Total
	Probable	Possible	Not Compatible*	No Symptoms	
Definite	14	4	1	1	20
Probable	74	0	0	0	74
Possible	0	13	0	0	13
Not Covid-19	0	0	10	0	10
No Symptoms	0	0	0	704	704
Total	88	17	11	705	821

*Clinical Case Classification was performed blinded to study arm and without lab-testing results. The final classification incorporates lab PCR testing results.

Category	N	Clinical Case Definition Syndromic Details (without lab results)
Probable Cases, Pulmonary	54	Cough (n=48), or Shortness of breath (n=19) or Difficulty breathing (n=2)
Probable Cases, non-Pulmonary	34	2 or more symptoms of: fever, chills ¹ , rigors ¹ , myalgia, headache, sore throat, new olfactory and taste disorder.
Possible Cases²	17	Compatible symptom(s) and epidemiologic link
		Sore throat (n=7) of whom 3 had nasal symptoms, Anosmia alone (n=3), myalgia alone (n=2), fever with nasal congestion (n=1), fatigue (n=2) with 1 rhinorrhea, diarrhea off study medicines (n=1), diarrhea with rhinorrhea (n=1),
Adjudicated as Not Compatible as Covid-19 Cases³	11*	Isolated symptoms of headache (n=3), diarrhea (n=4), nasal congestion (n=2), diffuse pruritic maculopapular rash lasting 10 days (n=1), nasal congestion with rhinorrhea (n=1)*.

* One case of nasal congestion with rhinorrhea was lab confirmed PCR-positive.

¹ Surveys did not directly query for chills or rigors, but there was a free text field for other symptoms. The case numbers include assignment of free text descriptions to the most similar symptom terminology.

² By the U.S. case definition, the “Possible Cases” are actually considered a “Probable case” due to the epidemiologic linkage. This possible classification is used to distinguish from the more robust symptom-complex presentation as all cases had PCR+ epidemiologic linkage. Of four adjudicated as possible cases using the clinical case definition alone but who were PCR positive (i.e. definitive Covid-19), they had isolated symptoms of: fatigue (n=1), myalgia (n=1), and anosmia and lack of taste (n=2).

When excluding 10 Possible cases with only one Covid-19 compatible symptom and without lab confirmation, incidence of new Covid-19 did not differ between those receiving hydroxychloroquine at 10.4% (43 of 414) versus placebo at 12.5% (51 of 407; P=0.34).

³ While all of these symptoms could possibly occur with Covid-19, some such as diarrhea and headache also overlap with side effect profile of hydroxychloroquine. Particularly when these symptoms occurred during the 5 days of study medicine administration and stopped after day 5, the blinded adjudication process thought these isolated symptoms were less compatible with Covid-19 and more compatible with medication side effects. When diarrhea occurred or persisted after 5 days, these were considered possible. All adjudications were blinded to study arm.

The total number of symptoms by study arm is presented in the manuscript, Table 2. Inclusion of all new self-reported possible Covid-19 symptoms (i.e. without any adjudication) narrows the events observed between hydroxychloroquine and placebo groups (13.8% vs. 14.6%, P=0.84). Events adjudicated as probable Covid-19 compatible illness by the U.S. case definition are also consistent with the World Health Organization case definition.³

Case Adjudication Process

We used the US clinical case classification, as the basis for adjudication.² Participants met the classification with their symptoms complex (“Probable”), had only 1 COVID-related symptom (“Possible”), or had other non-COVID symptoms which are not part of the case definition (Non-cases). Four infectious diseases physicians discussed ahead of time the use of the case definition, obtained consensus on the case definition, and then did the adjudications. Most adjudications were straight forward, as counting PCR+, cough, dyspnea, or >2 non-pulmonary COVID symptoms, this was 94 of 117 events (i.e. confirmed or probable Covid-19 per the case definition). The main role of adjudication was translating free-text descriptions into the nearest symptom. For example “difficulty breathing” was counted as the shortness of breath category.

The events we adjudicated as non-COVID by case definition were: isolated symptoms of headache (n=3), diarrhea (n=4) while receiving study medication, nasal congestion (n=2), diffuse pruritic maculopapular rash lasting 10 days (n=1), nasal congestion with rhinorrhea (n=1). The “nasal congestion with rhinorrhea” turned out to be PCR positive (i.e. “confirmed” as the final diagnosis). The rash could be COVID, based on some emerging dermatology case series info, but more conservatively, this was viewed as more likely to be a drug-allergy.

Table S3. Case Classification by Study Arm (Confirmed, Probable, Possible, Non-Covid-19)

Outcome	Hydroxychloroquine (N=414)	Placebo (N=407)
Confirmed or Probable Covid-19	49 (11.8%)	58 (14.3%)
Lab-confirmed Diagnosis	11 (2.7%)	9 (2.2%)
Probable Covid-19 compatible illness	32 (7.7%)	42 (10.3%)
Possible Covid-19 compatible illness*	6 (1.5%)	7 (1.0%)
Non-Covid-19 related symptoms	8 (1.9%)	2 (0.5%)
Death or cardiac arrhythmia	0 (0%)	0 (0%)

Final adjudications based on information provided above in Table S2.

* “Possible cases” as defined herein for this clinical trial also officially meet the U.S. clinical case definition as Probable Covid-19 due to their epidemiologic linkage to a PCR-positive index case with compatible illness.² A distinction is made within this manuscript to separate “possible” from “probable” cases, due to the more robust symptom complex of probable cases.

Table S4. Diarrhea

Diarrhea is not included as a symptom in the U.S. clinical case definition.¹

Overall, 28 participants reported diarrhea. The questioning of diarrhea was not detailed as to frequency and was self-identified. Thus, be aware that this is not defined as per a strict research definition of diarrhea. Free text descriptions varied from loose stool to significant >6 stools per day. The distribution of diarrhea in association with other symptoms was as follows.

- 16 cases also had pulmonary symptoms of cough (n=15) or shortness of breath (n=6)
- 12 cases reported diarrhea without pulmonary symptoms
 - 6 were associated with 2 or more symptoms of fever (n=4), headache, (n=2), sore throat (n=4), fatigue (n=4), myalgia (n=3) = Probable Cases per clinical case definition without diarrhea informing case adjudication.
 - 1 was associated with rhinorrhea = Possible Case
 - 1 was prolonged, continuing after discontinuation of study medicine and associated abdominal cramping = Possible Case
 - 4 were diarrhea / loose stool alone within the first 5 days and were rated as non-cases due to being possible side effects of the study medicine. All adjudications were blinded to study arm.

Table S5. Baseline Demographics for Asymptomatic and Exposed Cohort

	Hydroxychloroquine	Placebo
No. Participants	414	407
Age, years, median (IQR)	41 (33, 51)	40 (32, 50)
Weight, pounds, median (IQR)	165 (140, 190)	168 (140, 200)
Biologic Sex		
Male	192 (46.4%)	197 (48.4%)
Female	218 (52.7%)	206 (50.6%)
Not Stated	4 (1.0%)	4 (1.0%)
Ethnicity (all that apply)		
White or Caucasian	245 (59.2%)	262 (64.4%)
Black or African American	19 (4.6%)	18 (4.4%)
Asian	92 (22.2%)	83 (20.4%)
Native Hawaiian or Pacific Islander	2 (0.5%)	2 (0.5%)
Hispanic or Latino	22 (5.3%)	23 (5.7%)
Native American or Alaska Native	2 (0.5%)	1 (0.2%)
Middle Eastern	11 (2.7%)	2 (0.5%)
South Asian	18 (4.3%)	20 (4.9%)
Other	6 (1.4%)	3 (0.7%)
Time from exposure to enrollment, days, median IQR	3 (2, 4)	3 (2, 4)
Current Smoker		
Yes	15 (3.6%)	12 (2.9%)
No	395 (95.4%)	391 (96.1%)
Not stated	4 (1.0%)	4 (1.0%)
Country		
Canada	10 (2.4%)	11 (2.7%)
United States	404 (97.6%)	396 (97.3%)
Regularly Taking Any of These Medications		
Losartan or other ARB	14 (3.4%)	15 (3.7%)
Aspirin	10 (2.4%)	13 (3.2%)
Ibuprofen/naproxen	8 (1.9%)	8 (2.0%)
Tylenol	8 (1.9%)	11 (2.7%)
None	290 (70.0%)	269 (66.1%)
Chronic Health Conditions (Mark All That Apply)		
High blood pressure	51 (12.3%)	48 (11.8%)
Diabetes	12 (2.9%)	16 (3.9%)
Cardiovascular disease	4 (1.0%)	2 (0.5%)
Cancer or malignancy	1 (0.2%)	2 (0.5%)
Chronic kidney disease	0 (0.0%)	3 (0.7%)
Asthma	31 (7.5%)	31 (7.6%)
Other chronic lung disease	3 (0.7%)	0 (0.0%)
Chronic liver disease	0 (0.0%)	0 (0.0%)
HIV	1 (0.2%)	0 (0.0%)
Transplant recipient	0 (0.0%)	1 (0.2%)
Corticosteroids, chemotherapy, immunosuppressive	2 (0.5%)	1 (0.2%)
Hepatitis B or C	1 (0.2%)	0 (0.0%)
Other	25 (6.0%)	31 (7.6%)
None	306 (73.9%)	290 (71.3%)

IQR= interquartile range of the 25th and 75th percentile.

Table S6. Subgroup Analysis of Risk of New Covid-19 Compatible Illness

Subgroup	Hydroxychloroquine (N=414)		Placebo (N=407)		Absolute Risk Difference (95% CI)
	N	N Events	N	N Events	
Overall	414	49	407	58	-.024 (-.070, 0.022)
Contact Type					
Household	125	18	120	25	-.064 (-.160, 0.031)
Healthcare Worker	275	31	270	33	-.009 (-.064, 0.045)
Biological Sex at Birth					
Male	192	19	197	24	-.023 (-.085, 0.039)
Female	218	30	206	33	-.023 (-.090, 0.045)
Age in years					
18-35	151	18	145	27	-.067 (-.149, 0.015)
36-50	159	19	171	26	-.033 (-.106, 0.041)
> 50	104	12	91	5	0.060 (-.017, 0.138)
Days from Exposure					
1	77	5	63	8	-.062 (-.161, 0.037)
2	100	12	106	18	-.050 (-.146, 0.046)
3	98	12	117	17	-.023 (-.114, 0.068)
4	138	20	121	15	0.021 (-.062, 0.104)
Medicine Adherence*					
100%	312	43	336	50	-.011 (-.065, 0.043)
< 100%	37	4	15	3	-.092 (-.318, 0.134)
Did not take	65	2	56	5	-.059 (-.144, 0.027)

* Study medicine adherence was a post-hoc identified subgroup. There was a non-statistically 1.1% reduction in Covid-19 compatible illness among those who had 100% adherence to the study medication. "Did not take" also includes those who did not answer the medicine adherence question (n=47 hydroxychloroquine, n=46 placebo).

"Days from Exposure" are from the day of highest risk exposure to trial enrollment; Day 1 = same day as enrollment. Highest risk exposure was defined when questioning as the day when: closest to a COVID-19 contact, for the longest time, and with the least personal protective equipment. After enrolling in the trial, study medicines were shipped overnight to participants, Monday-Saturday in the United States and Monday-Sunday in Canada. The median overall time from highest risk exposure to starting study medicine was 3 days (IQR, 2 to 4 days). The median time from last exposure to starting study medicine was 2 days (IQR, 2 to 4 days with the distribution being: 1 day n=141, 2 days n=275, 3 days n=177, 4 days n=154, 5 days n=58, 6 days n=15.) One participant was missing exposure time.

All persons were asymptomatic when starting the study medicine. 100 persons who developed symptoms prior to receipt of study medicine were excluded from this trial and analyzed with a companion trial on early treatment (Refer to Figure 1 Consort diagram).

Table S7. Symptoms Experienced During Follow-up

Any Symptom	Hydroxychloroquine	Placebo
Participants	414	407
New COVID-19 Compatible illness	49 (11.8%)	58 (14.3%)
COVID-related symptoms		
Cough	27 (55.1%)	21 (36.2%)
Shortness of Breath	10 (20.4%)	10 (17.2%)
Fever	17 (34.7%)	20 (34.5%)
Headache	20 (40.8%)	23 (39.7%)
Sore Throat	21 (42.9%)	22 (37.9%)
Fatigue	25 (51.0%)	28 (48.3%)
Myalgia (muscle aches)	19 (38.8%)	21 (36.2%)
Lack of Smell / Taste	12 (24.5%)	13 (22.4%)
Other non-specific symptoms		
Diarrhea	16 (32.7%)	9 (15.5%)
Rhinorrhea (runny nose)	15 (30.6%)	13 (22.4%)
Nasal Congestion	15 (30.6%)	12 (20.7%)
Other symptoms	16 (32.7%)	11 (19.0%)
Total Number of Symptoms		
None	1 (2.0%)	3 (5.2%)
One	5 (10.2%)	8 (13.8%)
Two	9 (18.4%)	14 (24.1%)
Three	4 (8.2%)	8 (13.8%)
Four	10 (20.4%)	6 (10.3%)
Five	5 (10.2%)	8 (13.8%)
Six or more	15 (30.6%)	11 (19.0%)

Values are N (%). Number of symptoms and list of symptoms is among those with new COVID-19 compatible illness.

Table S8. Impact of Zinc or Vitamin C on Incidence of Covid-19 compatible illness.

		Hydroxychloroquine		Placebo		
		N Events	% New Covid-19 (95% CI)	N Events	% New Covid-19 (95% CI)	
Zinc						
Yes		15	15.0% (0.0, 33.1)	13	15.3% (0.0, 34.9)	
No		34	10.8% (0.4, 21.3)	45	14.0% (3.8, 24.1)	
Vitamin C						
Yes		20	14.3% (0.0, 29.6)	27	20.8% (5.5, 36.1)	
No		29	10.6% (0.0, 21.8)	31	11.2% (0.1, 22.3)	
Treatment Differences						
		Hydroxychloroquine		Placebo		Risk Difference (95% CI)
		N	Events	N	Events	
Zinc						
Yes		100	15	85	13	-0.003 (-.107, 0.101)
No		313	34	323	45	-0.031 (-.083, 0.020)
Vitamin C						
Yes		140	20	130	27	-0.065 (-.156, 0.026)
No		274	29	277	31	-0.006 (-.058, 0.046)

The relative risk with zinc use was 1.23 (95%CI, 0.82 to 1.83).

The relative risk with vitamin C use was 1.60 (95%CI, 1.12 to 2.28).

This observational comparisons may suffer from confounding by indication, in that those who deemed themselves at highest risk of developing infection may have been more likely to additionally take either zinc or vitamin C. Regardless, there was no suggestion that zinc added to hydroxychloroquine had additional benefit. Among those randomized to hydroxychloroquine, those taking zinc had a 15.0% incidence of new Covid-19 versus 10.8% incidence of new Covid-19 without self-reported zinc use.

Zinc has received a great deal of attention as a potential adjunctive therapy to be used with hydroxychloroquine. A 2014 in vitro study by Xue et al. used human ovarian carcinoma cell culture to examine the interaction of chloroquine and ionic zinc.⁴ Xue found that chloroquine acts as a zinc ionophore, increasing cellular uptake of zinc in culture media and increasing the cytotoxic effect of chloroquine to cause the death of cancer cells at levels 30-fold higher than what would be achieved in plasma with our trial's dosing.^{4,5} Importantly, this lab experiment was not designed to emulate zinc levels in the average human body, but in a cell culture media which started with minimal zinc. North Americans have a very low prevalence of inadequate dietary zinc intake (<15% prevalence).⁶ Based on this sub-group analysis, we found no evidence of supplementary zinc intake had any effect on incidence of new Covid-19 compatible illness after high-risk exposure. The exact details of zinc formulation, dose, and duration were not queried, so this is not conclusive information.

Table S9. Effect of Baseline Comorbidities on new Covid-19 compatible illness

Comorbidity	Hydroxychloroquine		Placebo	
	N	% (95% CI)	N	% (95% CI)
	Events		Events	
Yes	15	13.9 (0.0, 31.4)	12	10.3 (0.0, 27.4)
No	34	11.1 (0.5, 21.7)	46	15.9 (5.3, 26.4)

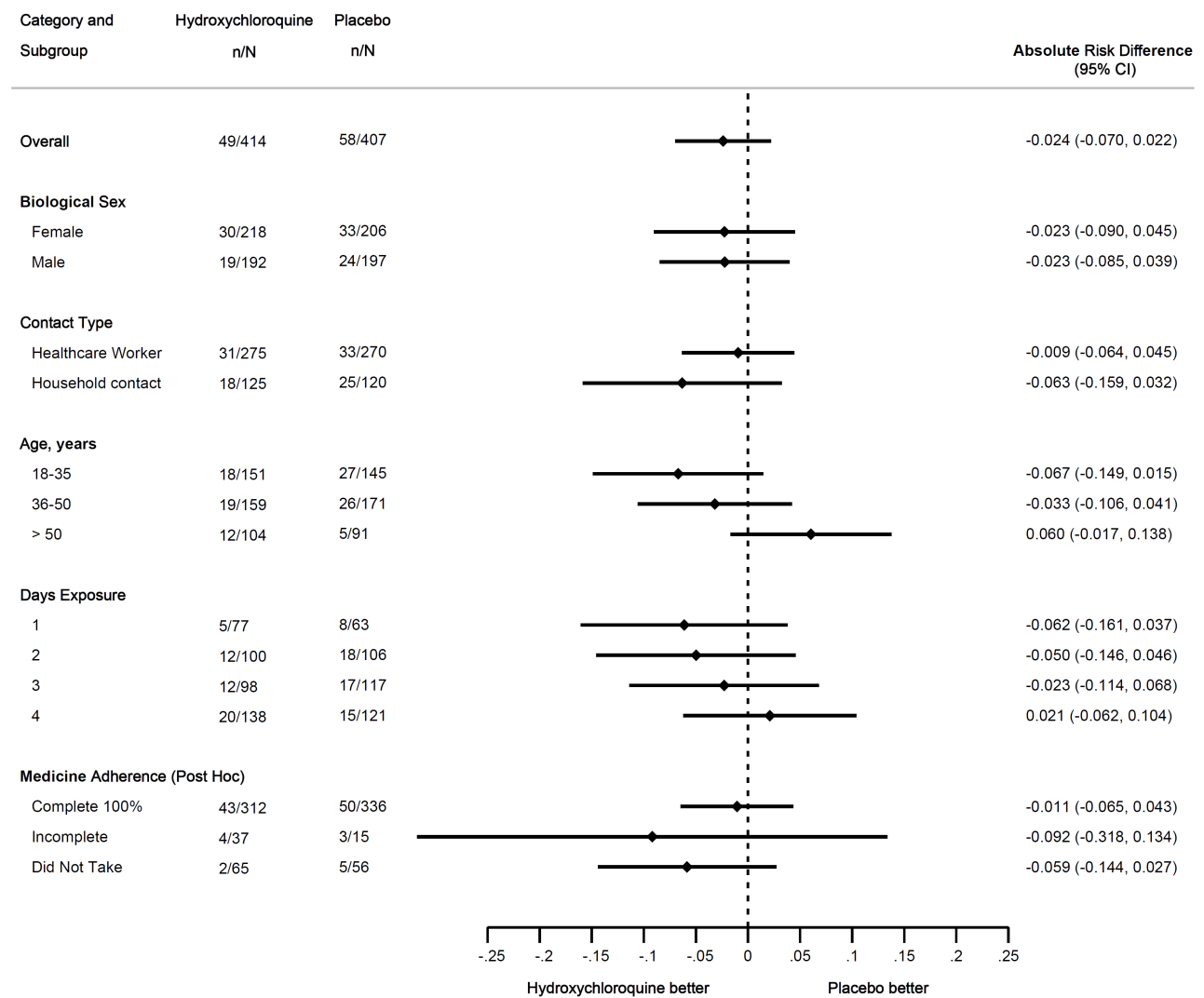
Treatment Differences

Comorbidity	Hydroxychloroquine		Placebo		Risk Difference 95% CI
	N	Events	N	Events	
Yes	108	15	117	12	0.036 (-.049, 0.122)
No	306	34	290	46	-.048 (-.102, 0.007)

Table S10. Baseline Demographics for those Lost to Follow-up with Unknown Vital Status.

Demographics of those Lost to Follow Up	Hydroxychloroquine N=36	Placebo N=33
Age, years, median, IQR	38 (31, 48)	39 (31, 51)
Weight, pounds, median IQR	157 (126, 182)	160 (135, 185)
Biologic Sex at birth		
Male	16 (44.4%)	12 (36.4%)
Female	19 (52.8%)	20 (60.6%)
Not Stated	1 (2.8%)	1 (3.0%)
Ethnicity (all that apply)		
White or Caucasian	14 (38.9%)	8 (24.2%)
Black or African American	3 (8.3%)	7 (21.2%)
Asian	13 (36.1%)	13 (39.4%)
Native Hawaiian or Pacific Islander	1 (2.8%)	0 (0.0%)
Hispanic or Latino	1 (2.8%)	4 (12.1%)
Native American or Alaska Native	0 (0.0%)	0 (0.0%)
Middle Eastern	0 (0.0%)	0 (0.0%)
South Asian	1 (2.8%)	2 (6.1%)
Other	2 (5.6%)	0 (0.0%)
Time from exposure to enrollment, days, median, IQR	3 (1, 5)	3 (2, 4)
Current Smoker	3 (8.3%)	2 (6.1%)
Country		
Canada	1 (2.8%)	0 (0.0%)
United States	35 (97.2%)	33 (100.0%)
Regularly Taking Any of These Medications		
Losartan or angiotensin receptor blocker	0 (0.0%)	0 (0.0%)
Aspirin	0 (0.0%)	2 (6.1%)
Ibuprofen/naproxen	1 (2.8%)	1 (3.0%)
Tylenol	0 (0.0%)	1 (3.0%)
None	33 (91.7%)	26 (78.8%)
Chronic Health Conditions (Mark All That Apply)		
High blood pressure	5 (13.9%)	1 (3.0%)
Diabetes	0 (0.0%)	1 (3.0%)
Cardiovascular disease	1 (2.8%)	0 (0.0%)
Asthma	1 (2.8%)	2 (6.1%)
Other chronic lung disease	1 (2.8%)	0 (0.0%)
Steroids, chemotherapy, immunosuppressants	1 (2.8%)	0 (0.0%)
Other	1 (2.8%)	1 (3.0%)
None	28 (77.8%)	27 (81.8%)

Values are N (%) or median (IQR). An internet search did not discover any obituaries for those lost to follow up with unknown vital status.

Figure S1. Forest Plot of A Priori Identified Subgroups

Those with non-healthcare, non-household contact had other occupational exposure.

Figure S2. Distribution of Symptoms for Lab-Confirmed Covid-19 Cases

Final Case Classification	Treatment Group	Cough	Fever	Shortness of Breath	Headache	Sore Throat	Fatigue	Myalgia	Anosmia	Diarrhea	Nasal Congestion	Rhinorrhea	Other Symptoms	Covid-19 Symptoms (N)
Confirmed	Black													0
Confirmed	Black													6
Confirmed	Black													5
Confirmed	Black													4
Confirmed	Black													0
Confirmed	Black													4
Confirmed	Black													5
Confirmed	Black													7
Confirmed	Black													6
Confirmed	Black													4
Confirmed	Black													1
Confirmed	Black													1
Confirmed	Black													8
Confirmed	Black													0
Confirmed	Black													1
Confirmed	Black													3
Confirmed	Black													5
Confirmed	Black													1
Confirmed	Black													1
Confirmed	Black													0

Treatment Group: Black = hydroxychloroquine; White = placebo.

The number of the Covid-19 symptoms is based on the April 6, 2020 U.S. clinical case definition.¹ Lab-confirmed cases reported PCR confirmation.

Number of Covid-19 symptoms limited to cough, shortness of breath fever, myalgia, fatigue, headache, sore throat, and lack of smell/taste. Symptoms of chills, rigors, and difficulty breathing were not directly queried on follow up surveys. Difficulty breathing in free text descriptions is included in shortness of breath. The trial commenced on March 17, whereas the U.S. case definition was not released until April 6, 2020, thus there was a limitation in not directly querying the full symptomology (e.g. chills, rigors, difficulty breathing), which may result in an under-count of the total number symptoms. The above plot includes three participants who reported symptoms after 14 days, marked with an asterisk (*).

Figure S3. Distribution of Symptoms for Probable Covid-19 Compatible Cases

[illegible]

The number of the Covid-19 symptoms is based on the April 6, 2020 U.S. clinical case definition.¹ Number of Covid-19 symptoms limited to cough, shortness of breath fever, myalgia, headache, sore throat, fatigue, and lack of smell/taste. Per the clinical case definition, Probable Cases had at least cough OR shortness of breath OR ≥ 2 of the other Covid-19 symptoms. Free text descriptions, categorized above as “other Covid-19 symptoms,” were also considered in the adjudication process.

Figure S4. Distribution of Symptoms for Possible Covid-19 and Non-Covid-19 Cases

Final Case Classification	Treatment Group	Cough	Fever	Shortness of Breath	Headache	Sore Throat	Fatigue	Myalgia	Anosmia	Diarrhea	Nasal Congestion	Rhinorrhea	Other Symptoms	Covid-19 Symptoms (N)
Possible	Black					Red							Red	1
Possible	Black					Red		Red					Red	1
Possible	Black					Red				Red		Red		0
Possible	Black					Red				Red		Red		1
Possible	Black					Red				Red		Red		0
Possible	Black					Red				Red	Red	Red		1
Possible	Black					Red				Red	Red			1
Possible	Black		Red			Red				Red	Red			1
Possible	Black					Red					Red			1
Possible	Black					Red	Red					Red		1
Possible	Black					Red								1
Possible	Black					Red			Red					1
Possible	Black					Red								1
Non-Case	Black				Red									1
Non-Case	Black				Red					Red				0
Non-Case	Black				Red									1
Non-Case	Black									Red	Red			0
Non-Case	Black									Red				0
Non-Case	Black									Red			Red	0
Non-Case	Black									Red				0
Non-Case	Black									Red				0
Non-Case	Black				Red									1
Non-Case	Black										Red			0

Treatment Group: Black = hydroxychloroquine; White = placebo.

The number of the Covid-19 symptoms is based on the April 6, 2020 U.S. clinical case definition.¹ All adjudications were blinded to study arm. Number of Covid-19 symptoms limited to cough, shortness of breath fever, myalgia, headache, sore throat, fatigue, and lack of smell. Chills, rigors, and difficulty breathing were not directly queried (but were assessed from free-text descriptions), thus there may be an undercount of Covid-19 related symptoms. Per our clinical case definition, “Possible Cases” had 1 possible Covid-19 symptom (meeting criteria for a compatible illness), but they did not have cough or shortness of breath.

“Non-cases” were adjudicated as unlikely to be Covid-19 with alternative diagnoses such as medication side effect, isolated headache, or upper respiratory tract infection being as likely.

When the excluding 13 possible Covid-19 cases, incidence of new Covid-19 did not differ with 10.4% (43 of 414) receiving hydroxychloroquine versus 12.5% (51 of 407) receiving placebo ($P=0.38$). Similarly, comparing anyone complaining of any new symptom by study arm (i.e. without any adjudication) did not alter the result ($P=0.84$), as presented in the manuscript’s Table 2.

Appendix References

1. Lothar SA, Abassi M, Agostinis A, et al. Post-exposure prophylaxis or pre-emptive therapy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): study protocol for a pragmatic randomized-controlled trial. *Can J Anaesth* 2020:*In Press*.
2. Council of State and Territorial Epidemiologists. Interim-20-ID-01: Standardized surveillance case definition and national notification for 2019 novel coronavirus disease (COVID-19). 2020. (Accessed 20 April 2020, at https://www.cste.org/resource/resmgr/2020ps/Interim-20-ID-01_COVID-19.pdf.)
3. World Health Organization. Global Surveillance for human infection with coronavirus disease (COVID-19). 2020. (Accessed 20 March 2020, at [https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-\(2019-ncov\)](https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)).)
4. Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ. Chloroquine is a zinc ionophore. *PLoS One* 2014;9:e109180.
5. Al-Kofahi M, Jacobson P, Boulware DR, et al. Finding the dose for hydroxychloroquine prophylaxis for COVID-19; the desperate search for effectiveness. *Clin Pharmacol Ther* 2020:*In Press*.
6. Wessells KR, Brown KH. Estimating the global prevalence of zinc deficiency: results based on zinc availability in national food supplies and the prevalence of stunting. *PLoS One* 2012;7:e50568.