Supplementary Material*

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Authorship Contributions:

DRB conceived of the trial and wrote the clinical protocol with input from RR, MRN, MFP, SML, CPS, and statistical input from NWE, ASB, and KHH. TCL collaborated and adapted the study for Canadian Sites with input from EGM, ISS, LJM, RZ, SAL, LEK, and GD. KHH and ASB generated the randomization sequence which was executed by DL. NWE and KHH conducted statistical analysis. ASB and SML developed the REDCap database with help from MFP, KAP, and ASB maintained the database. TCL adapted and maintained the database in Canada. CPS, AAN, MFP, KAP, ECO, and DAW did participant follow up for the U.S. site. EGM, ISS, LJM, RZ, SAL, LEK, and GD did participant follow up for the Canadian sites. Advertising and outreach was done by DRB, RR, SML, CPS, MFP, KAP, ASB, and AAN for the U.S. site. TCL, EGM, ISS, LJM, RZ, SL, LK, GD, NM, and MC did outreach for the Canadian sites. MA, DRB did case adjudication for trial entry when PCR tests were pending. The writing team vouches for the data, analyses, and content of the manuscript.

CPS and DRB wrote the first draft of the manuscript, and DRB was overall study guarantor with help from MFP, RR, SML, KAP, AAN and TCL. All authors reviewed, revised, and approved the final version of the manuscript. The FDA Investigational New Drug sponsor is DRB.

Additional Team Members' Contributions:

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Supplemental Methods 1: Case Definitions

U.S. Council of State and Territorial Epidemiologists (1)

Clinical Criteria for Reporting

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 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

Epidemiological Linkage Criteria for Reporting

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

Exposure: Close contact** with a person diagnosed with COVID-19; whereby c*lose 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.*

World Health Organization (WHO) COVID-19 Case Definition (2)

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Supplemental Methods 2: Additional Exclusion Criteria

The full list of exclusion criteria, included:

- Symptoms >4 days (per inclusion criteria)
- Age <18 years old
- Current hospitalization
- Hydroxychloroquine allergy
- Retinal eye disease
- Known glucose-6 phosphate dehydrogenase deficiency
- Known chronic kidney disease (stage 4 or 5 or receiving dialysis)
- Known porphyria
- Weight less than 40 kg
- Receiving chemotherapy
- Current use of hydroxychloroquine, chloroquine
- Current use of cardiac arrhythmia medicines of: flecainide; amiodarone; digoxin; procainamide; or sotalol.
- In Canada, additional exclusions mandated by regulatory authorities were: 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 (as below) (3)
- On April 20, 2020, additional U.S. exclusions were added for weight less than 50kg, structural or ischemic heart disease, personal or family history of cardiac QT prolongation, and QT-prolonging medications (as below).

Concomitant QT prolonging medications included current use of:

- 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

The prohibition of azithromycin and other QT prolonging medicines was at the express direction of the U.S. FDA as potentially unsafe in an outpatient clinical trial.

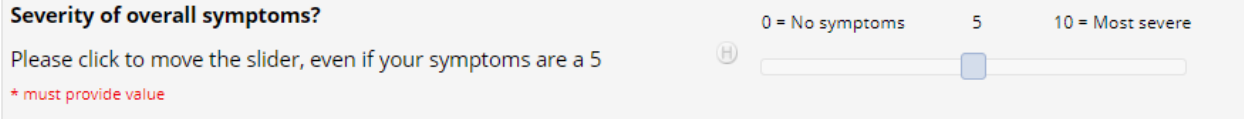
Supplemental Methods 3: Details on Primary Outcome Assessments

Treatment study primary outcome

Symptom severity scores were recorded with the online participant surveys at baseline, days 3, 5, 10 and 14 for those who responded "yes" to a survey question of: "Are you experiencing COVID-19 symptoms?"

i. Visual analog scale (0-10) for "overall symptom severity" was collected via a digital slider bar, which was marked with "0 = no symptoms"; 5 (placed in the middle); and "10 = severe symptoms"

ii. The exact wording of the question was as below: "Severity of overall symptoms?"



ii. For those who responded "no" to "Any symptoms experienced" the symptom severity score for that visit is assigned as zero.

i. For those hospitalized or with deaths, their symptom severity was scored as 10 if they did not respond to the visit survey.

ii. Individual symptoms were not scored, just the overall severity of symptoms.

Statistical analysis:

The primary analysis cohort includes all participants who contributed at least one follow-up survey with symptom data, so that change in symptom severity score could be assessed. A longitudinal mixed model was used to estimate the overall treatment difference between the treatment and control groups. The longitudinal mixed model (SAS PROC Mixed) considered study ID and treatment group as class variables, study visit as a continuous variable (based on actual date of survey completion) and was further adjusted for baseline symptom severity score. Change in symptom severity was assessed for each survey day (SAS PROC GLM), adjusting for baseline symptom severity score.

Three sensitivity analyses were performed:

a) Including only those with symptoms at baseline (thus excluding participants who were PCR positive at baseline with no reported symptoms);
b) Those who were symptomatic at consent (i.e., those randomized through the symptomatic strata only); and
c) Those who were asymptomatic at time of informed consent, randomized to the post-exposure trial, and then developed symptoms prior to study medication start date on Day 1.

An additional sensitivity analysis was performed using overall symptom severity scores (rather than change in scores) and which included the 68 participants with no follow-up symptom data. We used a log-link gamma-errors generalized linear mixed model and used new_score= score+1 to account for the inability of the log-gamma distribution to handle zero

values. With a log-gamma distribution, the estimate from the generalized linear mixed model is a difference of Hydroxychloroquine to placebo, so if there is no difference we would expect an estimate of 0. We generated 1000 estimates from simple random samples of n=400.

Median change in symptom score at each survey day is presented with interquartile range (IQR) as a sensitivity analysis with non-parametric statistics to assure that skewed data are not altering the result.

The primary outcome was also presented by subgroups (see Supplement Table 2) formed by COVID test results (confirmed PCR-positive vs. exposed to someone PCR-positive vs. other), age groups (18-35, 36-50, > 50), sex, and days from symptom onset to entry. These were the a priori subgroups defined in the Version 1.0 of the protocol.

Medication adherence was captured on study day 5. Another subgroup of interest is comparing the treatment groups for change in symptom severity score after day 5 by adherence reported at day 5 (<= 75% versus > 75%). For adherence, 75% equates to taking 15 or more of the 19 tablets of study medicine on time. Although not specified in the protocol, additional subgroup analyses were considered based on Zinc and Vitamin C use. These are presented due to the general public interest in zinc combined with hydroxychloroquine.

Note on the protocol:

The protocol is a combined protocol for both this trial, and our recently published companion trial using hydroxychloroquine as post-exposure prophylaxis (4). Some endpoints and statistical analyses refer to data published in the companion trial and are not applicable to this treatment trial.

Supplement Table 1. Detailed Baseline Characteristics by Treatment Group for Entire Enrollment Cohort

Characteristic	Hydroxychloroquine (N=244)	Placebo (N=247)
Age, median (IQR) -- years	41 (33, 50)	39 (31, 50)
Weight, median (IQR) – kg	73 (61, 85)	74 (64, 86)
Women -- N (%)*	136 (55.7)	130 (52.6)
Race/Ethnicity – N (%)		
White / Caucasian	118 (48.4)	117 (47.4)
Black or African American	9 (3.7)	6 (2.4)
Asian or South Asian	94 (38.5)	102 (41.3)
Hispanic or Latino	15 (6.2)	13 (5.3)
Middle Eastern	3 (1.2)	7 (2.8)
Native Hawaiian or Pacific Islander	3 (1.2)	2 (0.8)
Native American or Alaska Native	2 (0.8)	1 (0.4)
Other / Not Stated	6 (2.5)	7 (2.8)
Canadian – N (%)	20 (8.2)	18 (7.3)
Current smoker -- N (%)	10 (4.1)	11 (4.5)
Healthcare worker -- N (%)	132 (54.1)	128 (51.8)
Household contact -- N (%)	59 (24.2)	82 (33.2)
Comorbidities --- N (%)		
None	163 (66.8)	175 (70.9)
Hypertension	27 (11.1)	27 (10.9)
Diabetes	11 (4.5)	8 (3.2)
Asthma	30 (12.3)	21 (8.5)
Cardiovascular disease	4 (1.6)	2 (0.8)
HIV	1 (0.4)	0 (0.0)
Chronic lung disease	1 (0.4)	1 (0.4)
Chronic liver disease	1 (0.4)	1 (0.4)
Hepatitis B or C	1 (0.4)	2 (0.8)
Chronic immunosuppressants	0 (0.0)	3 (1.2)
Other	31 (12.7)	25 (10.1)
Asymptomatic at time of Consent	48 (19.7)	52 (21.1)
Current Symptoms--- N (%)	235 (96.3)	241 (97.6)
Cough	164 (67.2)	168 (68.0)
Fever	98 (40.2)	99 (40.1)
Shortness of breath	84 (34.4)	91 (36.8)
Headache	127 (52.0)	118 (47.8)
Sore throat	100 (41.0)	106 (42.9)
Fatigue	132 (54.1)	125 (50.6)
Muscle aches	115 (47.1)	103 (41.7)
Lack of Smell	34 (13.9)	35 (14.2)
Rhinorrhea	55 (22.5)	53 (21.5)
Diarrhea	53 (21.8)	52 (21.1)
Nasal Congestion	38 (15.6)	49 (19.8)
Final COVID-19 test result		
Positive	89 (36.5)	80 (32.4)
Negative	40 (16.4)	29 (11.7)
Pending	26 (10.7)	22 (8.9)
Not available / Not done	89 (36.5)	115 (46.6)

* 0.0% (0 of 266) were pregnant and 1.1% (3 of 266) were breastfeeding at enrollment. Values are N (%) or median (IQR). Supplement Table 9 provides the comparison between those providing data for primary endpoint with follow up surveys versus not providing any follow up symptom severity data.

Supplement Table 2. Subgroups Analysis

	Hydroxychloroquine		Placebo		Difference in Symptom Severity			Interaction
Subgroup	**N**	**Mean Change (SE)**	**N**	**Mean Change (SE)**	**Relative Difference**	**Absolute Difference**	**95% CI**	**P-value[2]**
Biological Sex								0.28
Male	88	-2.88 (0.19)	94	-2.38 (0.18)	21.0%	-0.50	-1.02, 0.03	
Female	123	-2.38 (0.16)	115	-2.27 (0.17)	4.8%	-0.11	-0.56, 0.34	
Age in years								0.73 (0.060)
18-35	69	-2.89 (0.20)	83	-2.73 (0.18)	5.9%	-0.16	-0.68, 0.36	
36-50	94	-2.48 (0.17)	78	-2.20 (0.19)	12.7%	-0.28	-0.78, 0.23	
>50	49	-2.36 (0.30)	50	-1.91 (0.30)	23.6%	-0.45	-1.27, 0.38	
SARS-CoV-2 PCR Testing								0.51
PCR Confirmed	73	-2.21 (0.23)	72	-2.10 (0.23)	5.2%	-0.11	-0.75, 0.52	
Probable COVID-19	139	-2.80 (0.14)	139	-2.45 (0.14)	14.7%	-0.36	-0.74, 0.03	
Exposure Contact Status								0.51
PCR positive	134	-2.49 (0.15)	146	-2.30 (0.15)	7.8%	-0.18	-0.60, 0.23	
Not confirmed/ unknown	78	-2.82 (0.20)	65	-2.38 (0.22)	18.5%	-0.44	-1.03, 0.15	
Final Diagnosis								0.68
PCR Confirmed	73	-2.21 (0.23)	72	-2.10 (0.23)	5.2%	-0.11	-0.75, 0.52	
Contact PCR Confirmed	92	-2.71 (0.16)	104	-2.44 (0.16)	11.1%	-0.27	-0.71, 0.18	
Probable Case Only	47	-3.01 (0.26)	35	-2.46 (0.30)	22.4%	-0.55	-1.33, 0.23	
Duration of symptoms [1]								0.28 (0.93)
<1 day	86	-1.91 (0.17)	83	-1.81 (0.18)	5.5%	-0.10	-0.58, 0.38	
1-2 days	67	-3.21 (0.24)	78	-2.55 (0.22)	25.9%	-0.66	-1.29, -0.02	
3-4 days	59	-2.89 (0.24)	50	-2.88 (0.26)	0.2%	-0.00	-0.69, 0.68	
Medicine Adherence								0.081 (0.052)
≥ 75% (>15 of 19)	165	-2.57 (0.13)	169	-2.15 (0.13)	19.5%	-0.42	-0.78, -0.06	
< 75% (1-14 tablets)	38	-2.70 (0.35)	25	-3.18 (0.44)	-15.1%	0.48	-0.63, 1.60	
Zinc Use								0.153
Yes	63	-2.55 (0.22)	53	-2.62 (0.24)	-3.1%	0.08	-0.58, 0.73	
No	143	-2.63 (0.15)	147	-2.17 (0.14)	21.5%	-0.46	-0.87, -0.06	
Vitamin C Use								0.048
Yes	101	-2.51 (0.18)	101	-2.55 (0.18)	-1.6%	0.04	-0.45, 0.54	
No	105	-2.69 (0.17)	99	-2.04 (0.17)	31.9%	-0.65	-1.12, -0.17	

Estimated in longitudinal mixed model adjusted for baseline severity score. P-value for trend of continuous variables are in parentheses. Medication adherence, zinc, and vitamin C use are post-hoc subgroups not specified in the protocol but identified by blinded investigators, prior to data analysis. The diagnostic testing results include results which returned after enrollment.

[1] Duration of antecedent symptoms. As a continuous variable, there was not a significant interaction between randomized treatment group and days of antecedent symptoms (interaction P=0.93). Without considering any potential interaction or adjusting for multiple comparisons, there was a marginally statistical difference in those with 1-2 days of symptoms, with receiving hydroxychloroquine being superior to placebo. We did not appreciate a biologic plausibility that would explain such a response versus random variation within a small subgroup. While randomization is equal in the overall trial; for small subgroups randomization may not be equal. Comparing those randomized to hydroxychloroquine to those randomized to placebo among those with 1-2 days of symptoms, hydroxychloroquine participants were more likely to have probable disease (73% vs. 56%) and less likely lab-confirmed disease (27% vs. 44%) (P=0.04); older by a median of 5 years (P=0.03), and had similar study medicine adherence (P=0.57) and biologic sex (P=0.13).

We would caution against over-interpretation of subgroup analyses. Notably, in the post-hoc subgroup analysis on medication adherence, those with >75% adherence randomized to hydroxychloroquine did statistically better than placebo . However, this group did not improve any more than the non-adherent hydroxychloroquine group nor the non-adherent placebo group. Another subgroup that could be over-interpreted is symptom duration. There was no difference in the treatment effect across the three groups (i.e. heterogeneity) of symptom duration (P=0.28). Thus, it would be generally inappropriate to select one subgroup, such as those with 1-2 days of symptoms, to claim a different effect based on a marginal p-value (5). Both of these point to problems with subgroup analyses where small sample sizes, which may not be equally randomized within the subgroup, can be over-interpreted (5). When performing multiple subgroup analyses, the probability of a false positive finding can be substantial (5,6).

Noteworthy for future research, the resolution of symptom severity slowed with increasing age, yet those >50 years of age had the largest, non-statistical relative difference with hydroxychloroquine use (23.6%). This was a small subgroup, but this may be a target population for future outpatient trials.

Supplement Table 3. Medication Adherence and Side Effects by Group at Day 5.

	Hydroxychloroquine (N=212)	Placebo (N=211)	P-value
Study medicine adherence -- N (%)			
Day 5 Survey responses for adherence	203	194	
100% adherence	157 (77.3)	166 (85.6)	
75-99% adherence	8 (4.0)	3 (1.6)	
<75% adherence	16 (7.9)	12 (6.2)	
Never started study medication	22 (10.8)	13 (6.7)	
Side effects summary -- N (%)			
Any side effects	92 (43.4)	46 (21.8)	<0.001
Side effects -- N (%)			
Upset stomach / nausea	66 (31.1)	26 (12.3)	
Diarrhea, other GI symptoms, vomiting	50 (23.6)	20 (9.5)	
Neurologic (Nervousness, irritability, dizziness, or vertigo)	20 (9.4)	13 (6.2)	
Skin reaction, rash	6 (2.8)	2 (1.0)	
Ringing in ears	8 (3.8)	5 (2.4)	
Allergic reaction, self-reported	5 (2.4)	0 (0)	
Changes in vision	4 (1.9)	5 (2.4)	
Warmth, hot flashes, night sweats	2 (0.9)	0 (0)	
Headache	2 (0.9)	0 (0)	
Taste, dry mouth	0 (0)	1 (0.5)	
Heart racing, anxiety, panic attack	0 (0)	1 (0.5)	
Cardiac Arrhythmia	0 (0)	0 (0)	

Denominator of the table is among those completing follow up surveys through day 5.

Supplement Table 4. Symptom Severity Score Mean Change from Baseline

A. Primary Outcome: Mean Change in Symptoms Severity Score from Baseline

	Hydroxychloroquine			Placebo			Difference (Hydroxychloroquine - Placebo)			
	N	Mean	95% CI	N	Mean	95% CI	Absolute	95% CI	Relative	P-value
Day 3	151	-1.60	-1.96, -1.25	154	-1.33	-1.68, -0.98	-0.27	-0.77, 0.23	20.3%	0.29
Day 5	204	-2.22	-2.53, -1.90	194	-2.05	-2.37, -1.73	-0.17	-0.63, 0.28	8.2%	0.46
Day 10	187	-3.06	-3.35, -2.76	176	-2.63	-2.94, -2.33	-0.42	-0.86, -0.00	15.9%	0.050
Day 14	201	-3.36	-3.62, -3.09	194	-3.08	-3.35, -2.81	-0.28	-0.66, 0.10	9.1%	0.150
Overall	**212**	**-2.60**	**-2.84, -2.36**	**211**	**-2.33**	**-2.57, -2.09**	**-0.27**	**-0.61, 0.07**	**11.6%**	**0.117**

B. Sensitivity Analysis: Median Change in Symptoms Severity Score from Baseline

	Hydroxychloroquine		Placebo		Difference (Hydroxychloroquine - Placebo)		
Survey Day	N	Median [IQR]	N	Median [IQR]	Absolute Difference	Relative Difference	P-value
Day 3	151	-1.50 [-3.20, 0.10]	154	-1.20 [-2.80, 0.20]	-0.30	25.0%	0.39
Day 5	204	-2.10 [-3.60, -0.45]	194	-2.00 [-4.00, 0.00]	-0.10	5.0%	0.75
Day 10	187	-2.80 [-5.00, -1.30]	176	-2.70 [-5.00, -0.80]	-0.10	3.7%	0.26
Day 14	201	-3.10 [-5.50, -1.70]	194	-3.15 [-5.00, -1.50]	0.05	-1.6%	0.34

P-values by Kruskal-Wallis test.

Supplement Table 5. Post-hoc Sensitivity Analyses of Change in Symptom Severity Score from Baseline

	Hydroxychloroquine			Placebo			Difference (Hydroxychloroquine - Placebo)			
	N	Mean	95% CI	N	Mean	95% CI	Absolute	95% CI	Relative	P-value
With symptoms[1]	207	-2.61	-3.15, -2.08	206	-2.34	-2.87, -1.80	-0.28	-0.62, 0.07	12.0%	0.116
Symptomatic at Consent [2]	165	-2.73	-3.01, -2.45	159	-2.55	-2.84, -2.26	-0.18	-0.59, 0.22	7.1%	0.38
New Symptoms on Day 1 [3]	47	-2.01	-2.45, -1.58	52	-1.49	-1.91, -1.08	-0.52	-1.12, 0.08	34.9%	0.092
Adjusted for Country and Strata [4]	212	-2.39	-2.81, -2.07	211	-2.17	-2.53, -1.80	-0.27	-0.61, 0.07	12.4%	0.122

1 Only includes participants with baseline symptoms, excluding those PCR positive not reporting initial symptoms.

2 Participants who were randomized in the strata of being PCR-positive or symptomatic at time of informed consent at enrollment only;

3 Participants, who did not have any symptoms at time of informed consent, but who became symptomatic on Study Day 1 before receiving study medicine. Per the protocol, these persons were to be separately analyzed and included with the treatment trial for analysis. This is a separate randomization strata.

4 Adjusted for Country (Canada vs. USA) and randomization strata (symptomatic vs. asymptomatic at time of consent).

All mean change and estimated difference from longitudinal mixed model values were adjusted for baseline severity score. Relative Difference = (Hydroxychloroquine - Placebo)/Placebo.

Sensitivity Analysis Accounting for Missing Data:

An additional sensitivity analysis was performed using overall symptom severity scores (rather than change in scores) and which included the 68 participants with no follow-up symptom data. We generated 1000 estimates from simple random samples of n=400, and derived a mean difference of -0.17 overall symptom severity with a corresponding 95%CI of -0.39 to 0.06.

Supplement Table 6. Baseline Information by Contact Type

	Household Contact N=106		Healthcare Worker N=241		Other Exposure [1] N=76		Overall N=423	
	No.	%	No.	%	No.	%	No.	%
Randomized to Intervention	45	42.5	124	51.5	43	56.6	212	50.1
COVID-19 test result								
Positive	15	14.2	53	22.0	54	71.1	122	28.8
Negative	9	8.5	32	13.3	1	1.3	42	9.9
Pending	11	10.4	30	12.4	3	3.9	44	10.4
Not done [2]	71	67.0	126	52.3	18	23.7	215	50.8
Symptoms at Baseline								
Cough	71	67.0	155	64.3	49	64.5	275	65.0
Fever	38	35.8	88	36.5	36	47.4	162	38.3
Shortness of breath	37	34.9	70	29.0	32	42.1	139	32.9
Headache	50	47.2	124	51.5	40	52.6	214	50.6
Sore throat	49	46.2	100	41.5	26	34.2	175	41.4
Fatigue	52	49.1	122	50.6	44	57.9	218	51.5
Muscle aches (Myalgia)	43	40.6	106	44.0	36	47.4	185	43.7
Lack of smell (Anosmia)	26	24.5	22	9.1	11	14.5	59	13.9
Diarrhea	19	17.9	48	19.9	19	25.0	86	20.3
Rhinorrhea	17	16.0	63	26.1	18	23.7	98	23.2
Nasal congestion	22	20.8	37	15.4	14	18.4	73	17.3
Has any symptom	104	98.1	237	98.3	72	94.7	413	97.6
Days since symptoms started								
<1	56	52.8	98	40.7	15	19.7	169	40.0
1	17	16.0	42	17.4	8	10.5	67	15.8
2	13	12.3	46	19.1	19	25.0	78	18.4
3	14	13.2	27	11.2	13	17.1	54	12.8
4	6	5.7	28	11.6	21	27.6	55	13.0
Median days [IQR]	0 [0, 2]		1 [0, 2]		2 [1, 4]		1 [0, 3]	

1 Non-household or occupational contact; or no known exposure with being PCR-positive.

2 First iteration of survey combined negatives and not done

Supplement Table 7. Duration of Symptoms prior to Enrollment

Exposure Group	N	Mean (SD)	Median	IQR
Lab Confirmed PCR+	145	2.2 (2.9)	2	0-3
Contact PCR+	196	1.3 (1.6)	1	0-2
Probable Case Only	82	1.0 (1.4)	0	0-2

Those with PCR-positive lab confirmation took an additional ~1 day to enroll into the trial from those who were symptomatic with an epidemiologic linkage to a PCR+ case.

Supplement Table 8. Association between Study Medicine Side Effects and COVID-19 Symptoms at Days 3 and 5

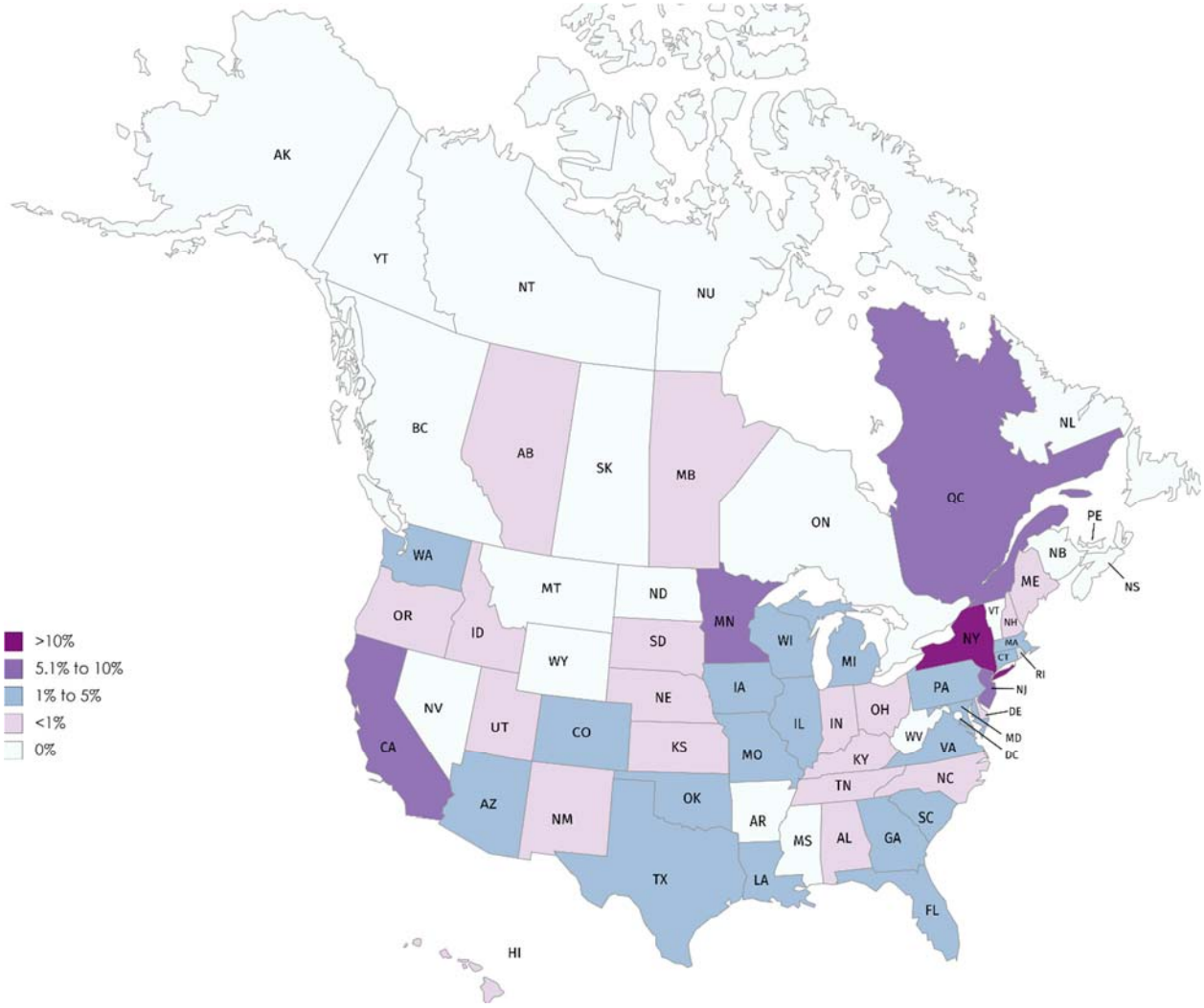
Survey Day	Medicine Side Effects	Hydroxychloroquine		Placebo	
		N	Symptomatic	N	Symptomatic
Day 3	Yes	66	44 (67%)	34	26 (76%)
	No	84	51 (61%)	120	82 (68%)
Day 5	Yes	92	55 (60%)	44	26 (59%)
	No	111	54 (49%)	150	88 (55%)

There was no association between the presence of reported medication side effects and reported COVID-compatible symptoms.

Supplement Table 9. Comparison of those not providing data for primary endpoint

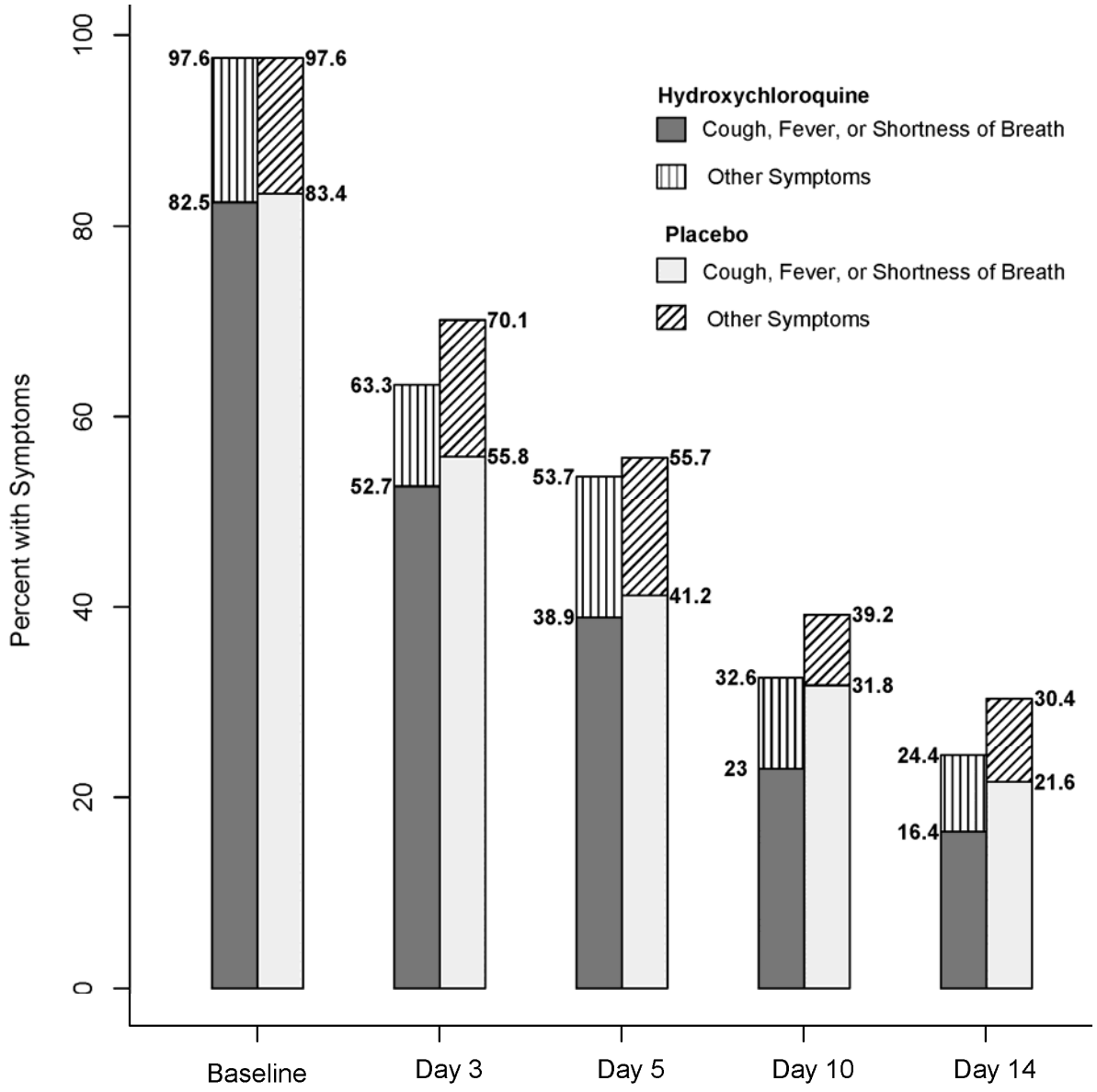
	Primary Endpoint (n=423)		Excluded (n=68)	
	No.	**%**	**No.**	**%**
Country				
Canada	38	9.0	0	0
US	385	91.0	68	100
Contact type				
Household contact	106	25.1	35	51.5
Healthcare worker	241	57.0	19	27.9
Other contact[1]	76	18.0	14	20.6
Age in years				
18-35	152	35.9	24	35.3
36-50	172	40.7	27	39.7
>50	99	23.4	17	25
Median years [IQR]	40 [32, 50]		42 [33, 51]	
Biological Sex				
Male	182	43.0	39	57.4
Female	238	56.3	28	41.2
Non-binary / Not stated	3	0.7	1	1.5
Randomization Strata				
Asymptomatic at Consent	99	23.4	1	1.5
Symptomatic at Consent	324	76.6	67	98.5
Weight, kg Median [IQR]	73.6 [63.6, 86.4]		75.0 [63.2, 82.7]	
Race/Ethnicity (all that apply)				
White or Caucasian	219	51.8	16	23.5
Black or African American	14	3.3	1	1.5
Asian	126	29.8	44	64.7
Native Hawaiian or Pacific Islander	1	0.2	4	5.9
Hispanic or Latino	25	5.9	3	4.4
Native American or Alaska Native	3	0.7	0	0
Middle Eastern	9	2.1	1	1.5
South Asian	24	5.7	2	2.9
Other	7	1.7	0	0
Not stated	5	1.2	1	1.5
Duration of symptoms, days				
<1	169	40.0	28	41.2
1-2	145	34.3	27	39.7
3-4	109	25.8	13	19.1
Baseline symptoms				
Cough	275	65.0	57	83.8
Fever	162	38.3	35	51.5
Shortness of breath	139	32.9	36	52.9
Headache	214	50.6	31	45.6
Sore throat	175	41.4	31	45.6
Fatigue	218	51.5	39	57.4
Muscle aches	185	43.7	33	48.5
Lack of smell	59	13.9	10	14.7
Cough, fever, dyspnea (have 2 of 3)	174	41.1	46	67.6
PCR Positive or Contact Positive	341	80.6	62	91.2

Supplement Figure 1. Distribution of Enrollment by Location



Trial enrollment occurred in 40 U.S. States and the Canadian provinces of Quebec, Manitoba, and Alberta. The percentages are of the total trial enrollment of 491 participants.

<u>Supplement Figure 2</u>. Proportion with Ongoing COVID-19 Symptoms

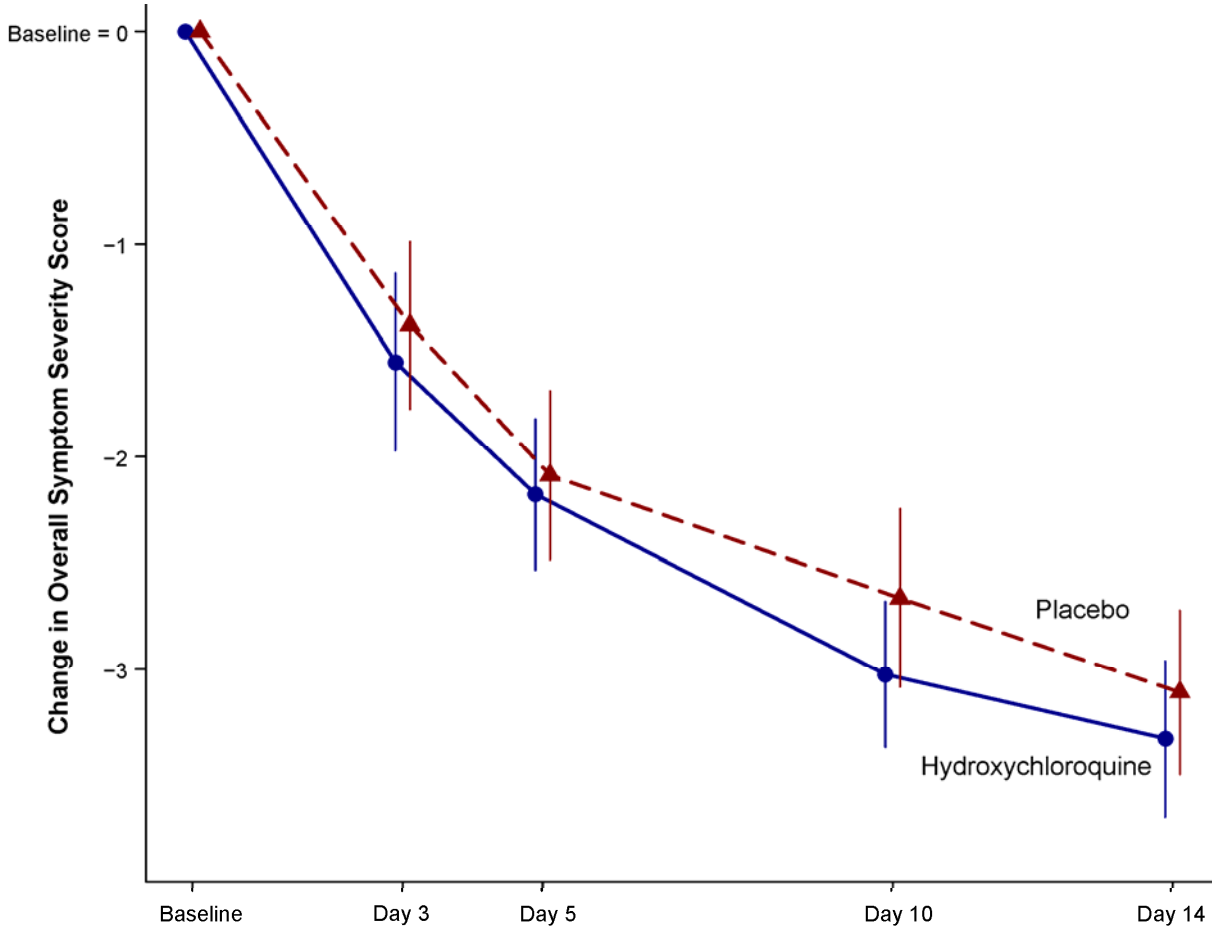


Number with data					
Hydroxychloroquine:	212	150	203	187	201
Placebo:	211	154	194	176	194

The stacked bar graph distinguishes the relative proportions of those with presentation of cough, fever, or shortness of breath versus only other Covid-19 related symptoms (e.g. myalgia, fatigue, anosmia, sore throat, headache, chills, or rigors).

There is no statistical difference between the groups in the proportion of participants with symptoms at Day 14 (P=0.21). An alternative way to consider the magnitude of effect is for every 50 people treated with hydroxychloroquine, 1 additional person might be symptom free at day 5, 3 additional persons might be symptom free at day 14, and 20 persons would experience medication side effect(s) with 4 discontinuing hydroxychloroquine due to intolerability in order to achieve this possible effect.

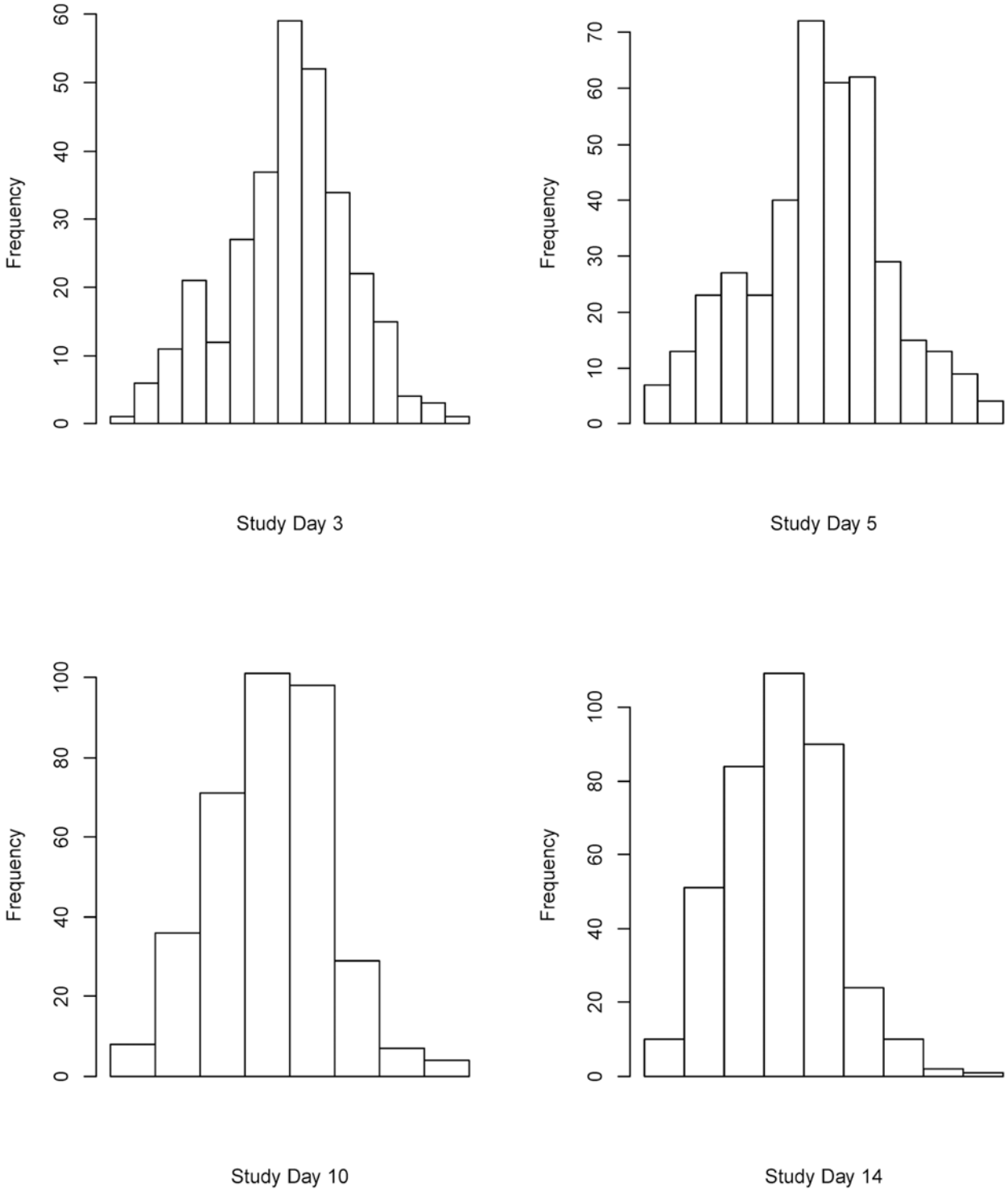
<u>Supplement Figure 3</u>. Change in Symptom Severity from Baseline on 10-point Visual Analog Scale



		Number of participants (% with increase in severity score):			
Hydroxychloroquine	212	151 (25%)	204 (16%)	187 (6%)	201 (9%)
Placebo	211	154 (27%)	194 (20%)	176 (16%)	194 (10%)
P−values, adjusted for baseline score:		0.29	0.46	0.05	0.15

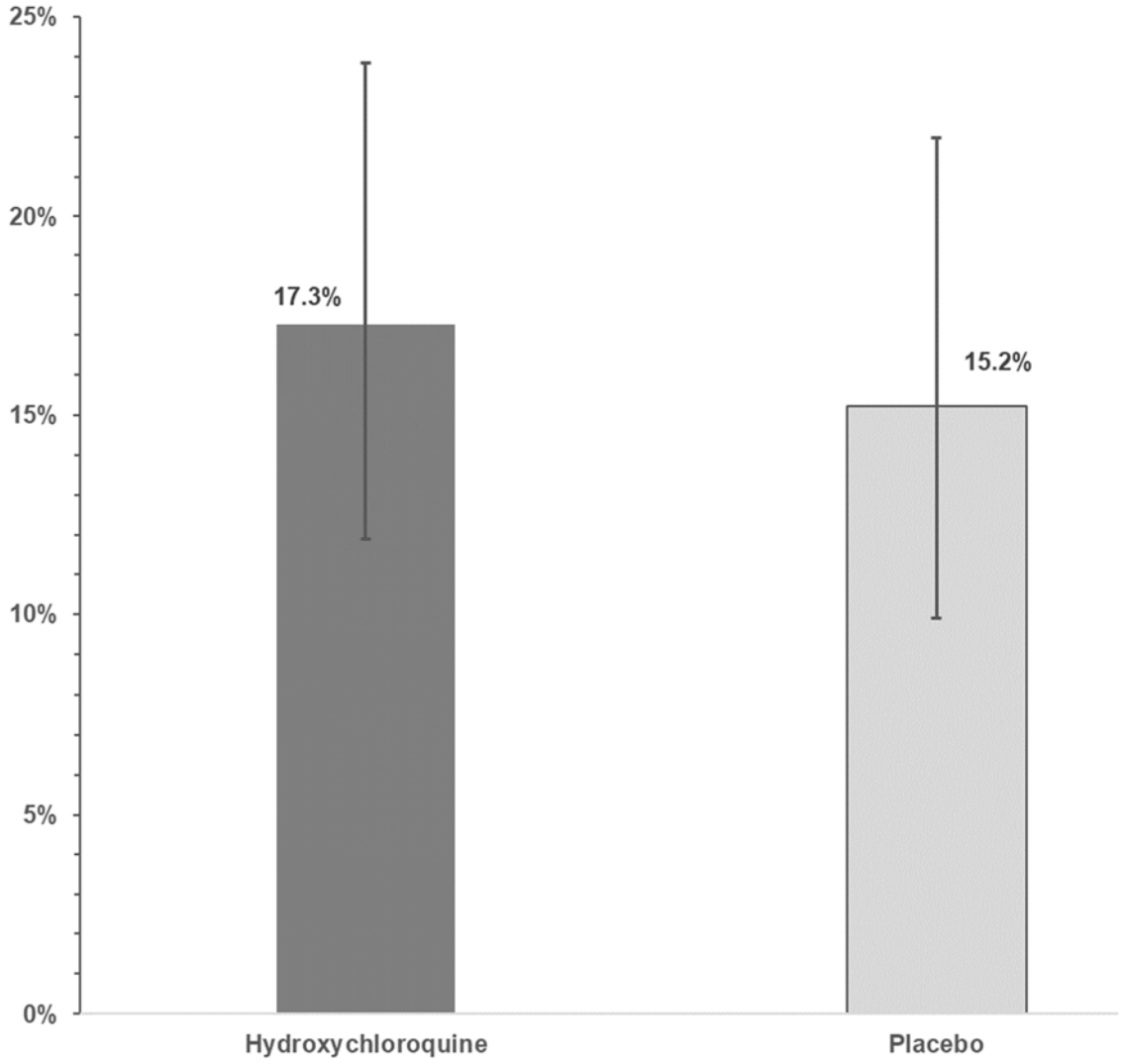
The figure displays the mean (95%CI) change in symptom severity score from baseline. The change in symptom severity score was normally distributed at each time point (Supplement Figure 4).

<u>Supplement Figure 4.</u> Histogram of Change in Severity Score by Study Day



Histograms demonstrate approximately normal distribution for the change in symptom severity score from baseline for each study survey day. Thus, using parametric statistics with the assumption of normal distribution is appropriate.

<u>Supplement Figure 5</u>. Secondary Transmission within Household



There was no impact on reducing secondary transmission. Of 319 participants with someone else living in their household, only 52 (16.3%) others became ill by day 14 (17% (29/168) hydroxychloroquine vs. 15% (23/151) placebo. The absolute difference is 2.0% (95%CI, -6.1% to 10.1%; P=0.65).

Supplement References

1. Council of State and Territorial Epidemiologists. Interim-20-ID-01: Standardized surveillance case definition and national notification for 2019 novel coronavirus disease (COVID-19). Available at: https://www.cste.org/resource/resmgr/2020ps/Interim-20-ID-01_COVID-19.pdf. Accessed 20 April 2020.

2. World Health Organization. Global Surveillance for human infection with coronavirus disease (COVID-19). Available at: https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov). Accessed 20 March 2020.

3. Lother SA, Abassi M, Agostinis A, Bangdiwala AS, Cheng MP, Drobot G, 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*. doi:10.1007/s12630-020-01684-7.

4. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. 2020; *In Press*. doi:10.1056/NEJMoa2016638.

5. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM**.** Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med. 2007; 357(21): 2189-94.

6. Lagakos SW**.** The challenge of subgroup analyses--reporting without distorting. N Engl J Med. 2006; 354(16): 1667-9.