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Authorship Contributions:

RR and DRB conceived of the trial. RR wrote the clinical protocol with the assistance of SML, CPS, DRB, MRN, JB, BR, PL and IM, and statistical input from ASB, NWE, and KHH. LJM collaborated and adapted the study for Canadian sites with input from DSM, DS and TCL and. KHH, ASB, and NWE conducted the statistical analyses, with the analysis being guaranteed by KHH. ASB developed the REDCap database with help from MFP, KAP, SML, and CPS. ASB maintained the database. TCL and EGM adapted the database in Canada. MLA, CPS, AAN, MFP, KAP, ECO, DAW, LJM, and RR did participant follow-up. Advertising and outreach were

done by SD, DRB, RR, SML, CPS, MFP, ASB, AAN, ECO, PL, DAW, LJM, SAL, DSM, GD, and RZ. RR, CPS and SML did case adjudication. Hydroxychloroquine drug levels sub-study was conceived by MRN, RR, DK, RZ, and levels were run by MRN. RR wrote the first draft of the manuscript and is the overall study guarantor with help from SML, DRB, CPS, MFP, KAP, ECO, AAN, and DAW. All authors reviewed and revised and approved the final version of the manuscript. The FDA Investigational New Drug sponsor is RR.

Steve Kirsch, David Baszucki and Jan Ellison Baszucki, the Rainwater Charitable Foundation, the Alliance of Minnesota Chinese Organizations, the Minnesota Chinese Chamber of Commerce, and the University of Minnesota provided funding but did not have a role in protocol development or monitoring. Rising Pharmaceuticals provided the hydroxychloroquine tablets.

Methods S1. Additional Exclusion Criteria

Additional exclusion criteria included, prior allergy or adverse reaction to chloroquine or hydroxychloroquine, known QT prolongation, G6PD deficiency, porphyria, prior retinal eye disease, chronic kidney disease (stage 4, 5, or dialysis), weight <40kg.

Current use of the following medications was contraindicated: hydroxychloroquine, chloroquine, flecainide, amiodarone, digoxin, procainamide, propafenone, artemether, lumefantrine, mefloquine, tamoxifen, or methotrexate.

In Canada, additional exclusions requested by Health Canada were: pregnancy, breastfeeding, severe diarrhea or vomiting, known cirrhosis with history of encephalopathy or ascites, current use of systemic chemotherapy, residing in a remote location not serviced by courier, ventricular arrhythmia, or history of sudden cardiac death, or QT prolonging medicines (dapsone, dofetilide, sotalol, levofloxacin, ciprofloxacin, moxifloxacin, azithromycin, clarithromycin, erythromycin, ketoconazole, itraconazole, amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, sertraline, bupropion, venlafaxine, haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone, methadone, or current use of sumatriptan or zolmitriptan if not prescribed "as needed").

Methods S2. Covid-19 Clinical Case Definition

Clinical case definition of Covid-19 was defined on April 5, 2020 by the US Council of State and Territorial Epidemiologists.[1]

Clinical Criteria for Reporting include at least two of the following symptoms:

- Fever
- Chills
- Rigors
- Myalgia
- Headache
- Sore throat
- New olfactory and taste disorders

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.

Participants meeting the above case definition are classified as "Probable" Covid-19 cases.

Epidemiological Linkage Criteria for Reporting

In a person with clinically compatible symptoms with one or more of the following exposures in the 14 days before onset of symptoms:

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

Participants were all considered to have epidemiological linkage given the inclusion criteria of being a high-risk healthcare worker with direct contact with Covid-19 patients. Thus, with this epidemiologic linkage, have one compatible symptom is defined as a probable case, per these guidelines. In our study, we defined these participants with one compatible symptom as 'possible' Covid-19.

Methods S3. Hydroxychloroquine drug concentrations

Participants who consented to the pharmacokinetic sub study were mailed Neoteryx® volumetric absorbed microsampling kits. Participants were provided detailed instructions on sample collection (https://www.neoteryx.com/home-blood-blood-collection-kits-dried-capillary-blood) and asked to fill two 10 microliter capillary tubes and return in provided packaging. Participants were asked to collect their sample immediately prior to their next scheduled dose of medication to provide consistency between participants and to evaluate trough concentrations. Participants self-reported time of collection and time of last dose of study medication prior to sample collection. Upon receiving the samples in the laboratory, they were stored in a cold room (4°C) with desiccants until sample analysis. Hydroxychloroquine has demonstrated stability greater than three weeks at room temperature.

Hydroxychloroquine concentrations were measured in dried blood similar to methods previously published.[2] Briefly, the tips of the capillary tubes containing the dried blood were removed and placed in microcentrifuge tubes along with internal standard solution. Samples were then vortexed before protein precipitation. Samples were then centrifuged (with tip remaining) to separate supernatant. Standards and quality control samples were prepared in an identical manner. Quantification of hydroxychloroquine was performed using high-performance liquid chromatograph coupled with a triple quad mass spectrometer. The assay was validated over the range of 50-2000 ng/mL with 3-day accuracy and precision $\leq$15%. Stability tests with samples stored at ambient temperature have confirmed stability up to three weeks post-collection.

Methods S4. Supplemental Methods

Hydroxychloroquine dosing

We hypothesized, based on pharmacokinetic simulations that twice-weekly dosing would be effective;[3] we also studied the well-established once weekly chemoprophylaxis dose due to its track record of safety and adherence as well as its deployment in non-experimental settings.[4,5]

Participants

On April 22, 2020 eligibility criteria expanded to include healthcare personnel working in congregate care facilities with Covid-19 cases (e.g., nursing homes or assisted living facilities) and urgent care. Pregnancy or breastfeeding were not exclusion criteria in the USA.

Setting

Other Canadian provinces pursued IRB approvals, but approvals were not completed by the time the trial closed.

Study Assessments

Participants hospitalized or pregnant at study termination had additional surveys administered to capture relevant longitudinal outcomes.

A pre-specified list of common hydroxychloroquine side effects and Covid-19 compatible symptoms were provided along with a free-text option where participants could specify side effects and/or symptoms experienced outside of those pre-specified. Participants who were non-responsive to follow-up surveys received email reminders, text messages, and phone calls to ascertain their outcomes. When all of these methods were unsuccessful, emergency contacts provided by the enrollee were contacted to establish the participant's vital status.

Randomization

Randomization occurred at research pharmacies in Minneapolis for participants in the United States and in Montreal for participants in Canada. The trial statisticians generated a

permuted block randomization sequence using variably sized blocks of two, four, and eight. A research pharmacist sequentially assigned participants. Treatment assignments were concealed from investigators and participants; the pharmacies were the only entities with access to the randomization sequence. Blinded hydroxychloroquine sulfate or placebo was dispensed and shipped over two days to participants by commercial courier. Placebo tablets (folic acid 400mcg in USA, 1000mcg in Canada) were similar but not identical in appearance.

Sample Size

We assumed loss to follow up of 5% in the treatment groups and 15% in the placebo groups, assuming healthcare workers might be able to discern hydroxychloroquine from placebo. We expected 117 Covid-19 events over 12 weeks.

Given the incidence of Covid-19 transmission to high-risk healthcare workers was unknown at the time of study initiation, we also planned for an *a priori* sample size re-estimation at the time of the first data and safety monitoring board (DSMB) review based on the observed event rate in the control group.

Statistical Methods

As sensitivity analyses, we included these participants, or excluded participants who became symptomatic during week one of the trial. As a secondary analysis, we planned to combine hydroxychloroquine arms and compare to placebo. *A priori* specified subgroups included: age, sex, and geographic region of exposure. We also planned to compare i) workers with a confirmed high-risk exposure event (one or more episodes of performing an aerosol-generating procedure with inadequate PPE) to workers without a confirmed high-risk exposure event, and ii) those with full medication adherence versus partial adherence. Inadequate PPE for aerosol-generating procedures was defined as not having both an N95 mask and eye protection, or not using a power air-purifying respirator (PAPR).

We defined symptomatic confirmed Covid-19 infection as having COVID-19-compatible illness with PCR testing within 4 days before onset of symptoms or within 11 days after onset of symptoms. If a participant had a positive PCR test, symptoms within 14 days of testing was considered symptomatic infection.

Full adherence was defined as 100% adherence at a minimum of 80% of surveys completed.

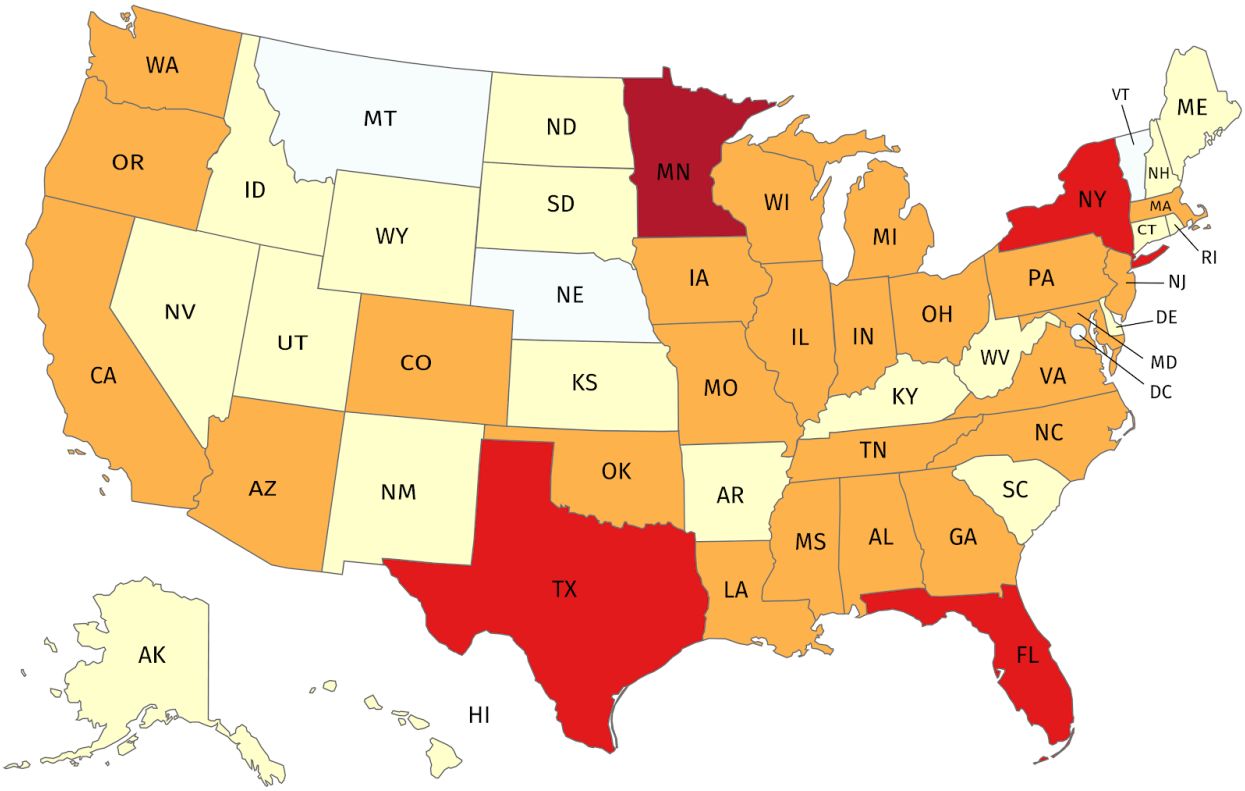
Subgroups

Subgroups of interest included age, sex, occupation (first responder vs. healthcare worker), occupational setting (congregate care setting vs. other), participants performing aerosol-generating procedures, high-risk (defined as performing aerosol-generating procedures with inadequate PPE), and geographic region.

Study Oversight

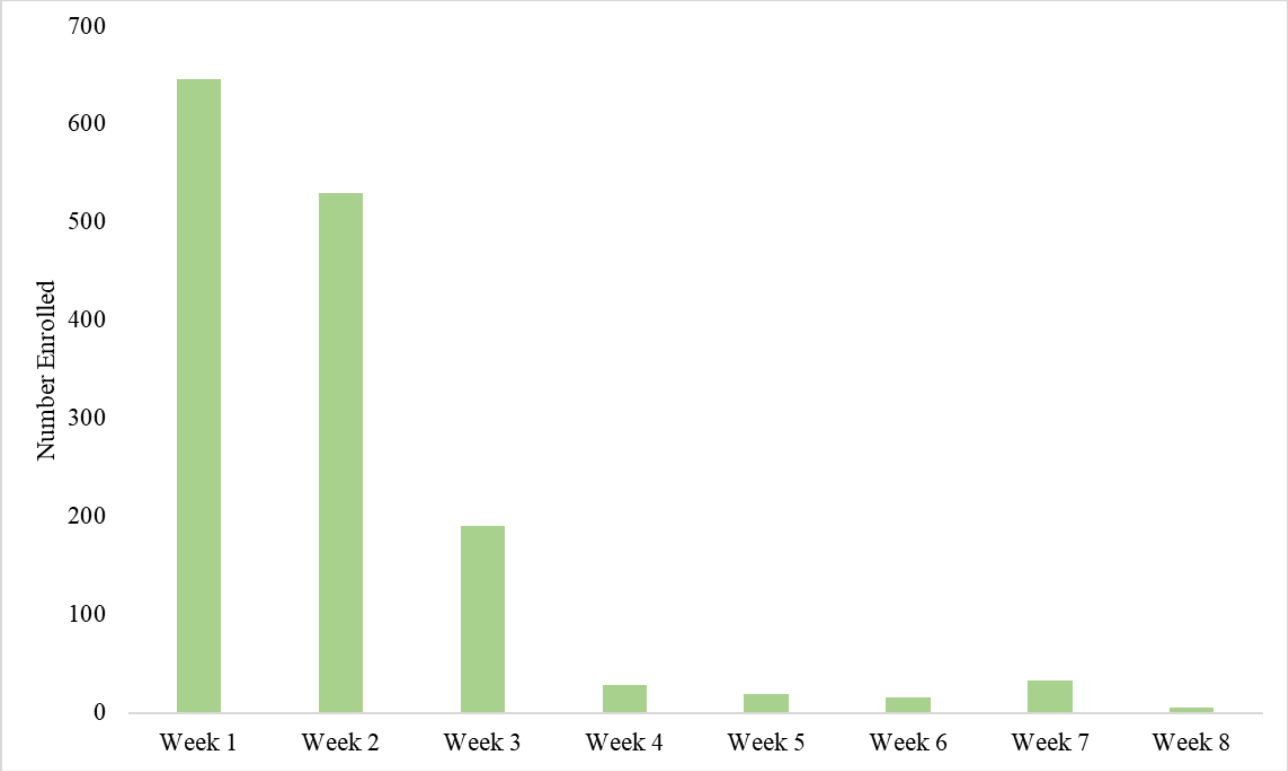
The trial was designed by the first author, in collaboration with all of the investigators. This trial was approved by the University of Minnesota Institutional Review Board, conducted under FDA Investigational New Drug (149252), and overseen by an independent DSMB. In Canada, the trial was authorized without objection by Health Canada (control number 238396), with ethics approval obtained from the University of Manitoba.

Figure S1. Map of Enrollment by State



Maroon >10%, Red = 5.1% to 10%, Orange 1 to 5%, Light yellow <1%, White 0% enrolled. An additional 3 participants (0.2%) were enrolled from Manitoba, Canada, and 3 participants (0.2%) from Puerto Rico.

Figure S2. Enrollment by Study Week



Supplemental Table 1. Baseline Demographics

	Placebo	Hydroxychloroquine once weekly	Hydroxychloroquine twice weekly
Number Randomized	494	494	495
Age in years, median (interquartile range)	40 (34, 48)	42 (35, 49)	41 (35, 49)
Weight in kilograms, median (interquartile range)	80 (68, 94)	79 (67, 93)	82 (68, 95)
Biologic Sex –no. (%)			
Male	252 (51.0%)	228 (46.2%)	235 (47.5%)
Female*	241 (48.8%)	261 (52.8%)	258 (52.1%)
Not Stated	1 (0.2%)	5 (1.0%)	2 (0.4%)
Ethnicity (all that apply) –no. (%)			
White or Caucasian	419 (84.8%)	431 (87.2%)	421 (85.1%)
Black or African	10 (2.0%)	5 (1.0%)	5 (1.0%)
Asian	29 (5.9%)	23 (4.7%)	23 (4.6%)
Native Hawaiian or Pacific Islander	1 (0.2%)	0 (0.0%)	1 (0.2%)
Hispanic or Latino	18 (3.6%)	18 (3.6%)	22 (4.4%)
Native American or Alaska Native	8 (1.6%)	4 (0.8%)	7 (1.4%)
Middle Eastern	4 (0.8%)	6 (1.2%)	5 (1.0%)
South Asian	12 (2.4%)	17 (3.4%)	18 (3.6%)
Other	4 (0.8%)	3 (0.6%)	1 (0.2%)
Current Smoker –no. (%)			
Yes	13 (2.6%)	17 (3.4%)	21 (4.2%)
No	480 (97.2%)	472 (95.5%)	472 (95.4%)
Not stated	1 (0.2%)	5 (1.0%)	2 (0.4%)
Regularly taking the following medications –no. (%)			
Losartan or other Angiotensin Receptor Blocker	21 (4.3%)	25 (5.1%)	26 (5.3%)

Aspirin	24 (4.9%)	29 (5.9%)	25 (5.1%)
Ibuprofen/naproxen	31 (6.3%)	39 (7.9%)	20 (4.0%)
Tylenol	18 (3.6%)	34 (6.9%)	21 (4.2%)
None	417 (84.4%)	390 (78.9%)	418 (84.4%)
Chronic Health Conditions (all that apply) –no. (%)			
High blood pressure	60 (12.1%)	79 (16.0%)	66 (13.3%)
Diabetes	14 (2.8%)	18 (3.6%)	18 (3.6%)
Cardiovascular disease	3 (0.6%)	5 (1.0%)	3 (0.6%)
Cancer or malignancy	1 (0.2%)	2 (0.4%)	1 (0.2%)
Chronic kidney disease	0 (0.0%)	0 (0.0%)	1 (0.2%)
Asthma	59 (11.9%)	46 (9.3%)	45 (9.1%)
Another chronic lung disease	1 (0.2%)	2 (0.4%)	3 (0.6%)
Chronic liver disease	0 (0.0%)	0 (0.0%)	0 (0.0%)
HIV	1 (0.2%)	1 (0.2%)	0 (0.0%)
Transplant Recipient	0 (0.0%)	0 (0.0%)	0 (0.0%)
Steroids, chemotherapy, immunosuppressants	4 (0.8%)	5 (1.0%)	1 (0.2%)
Hepatitis B or C	2 (0.4%)	1 (0.2%)	0 (0.0%)
Other	39 (7.9%)	55 (11.1%)	45 (9.1%)
None	336 (68.0%)	311 (63.0%)	335 (67.7%)
Participant Region –no. (%)			
Northeast	87 (19.7%)	82 (18.3%)	81 (18.0%)
Midwest + Canada	207 (46.9%)	216 (48.3%)	215 (47.7%)
South + Puerto Rico	91 (20.6%)	95 (21.3%)	88 (19.5%)
West	56 (12.7%)	54 (12.1%)	67 (14.9%)

* No participants reported pregnancy; thirty were breastfeeding at baseline.

Supplemental Table 2. Baseline Risk of Covid-19

	Placebo	Hydroxychloroquine once weekly	Hydroxychloroquine twice weekly
Number Randomized	494	494	495
Do you suspect you had COVID-19 disease at any point since the outbreak started? –no. (%)			
No	315 (63.8%)	299 (60.5%)	296 (59.8%)
Maybe, exposed to probable COVID19 case, NO symptoms	66 (13.4%)	80 (16.2%)	64 (12.9%)
Maybe, exposed to confirmed COVID19 case, NO symptoms	112 (22.7%)	115 (23.3%)	134 (27.1%)
Yes, exposed to probable COVID19 case, symptoms	0 (0.0%)	0 (0.0%)	1 (0.2%)
Yes, exposed to confirmed COVID19 case, symptoms	1 (0.2%)	0 (0.0%)	0 (0.0%)
Have you or will you have direct contact with COVID19 patients? –no. (%)			
Yes	494 (100.0%)	491 (99.4%)	494 (99.8%)
No	0 (0.0%)	3 (0.6%)	1 (0.2%)
Have you interacted with Covid19 patients when NOT wearing a mask (surgical, n95, PAPR) or NOT wearing a face shield? –no. (%)			
Yes	62 (12.6%)	69 (14.1%)	85 (17.2%)
No	432 (87.4%)	422 (85.9%)	409 (82.8%)
In a typical week, how many hours total are you in contact with patients? –no. (%)			
>14 hours	438 (88.7%)	452 (92.1%)	456 (92.3%)
1-14 hours	53 (10.7%)	37 (7.5%)	37 (7.5%)
0 hours	3 (0.6%)	2 (0.4%)	1 (0.2%)
Will you be involved in aerosol-generating procedures? –no. (%)			
Yes	410 (83.0%)	378 (77.0%)	377 (76.3%)
No	84 (17.0%)	113 (23.0%)	117 (23.7%)
How many aerosol-generating procedures do you perform per week, on average? –no.	10	9	9
PPE typically worn when performing aerosolizing generating procedures - no. (%)			
Surgical mask	162 (32.8%)	145 (29.4%)	142 (28.7%)

n95 or PAPR	385 (77.9%)	356 (72.1%)	357 (72.1%)
Face shield or eye mask	334 (67.6%)	312 (63.2%)	306 (61.8%)
Gloves	359 (72.7%)	340 (68.8%)	329 (66.5%)
Gown	316 (64.0%)	301 (60.9%)	294 (59.4%)
None reported	3 (0.6%)	5 (1.0%)	5 (1.0%)
Occupation –no. (%)			
Emergency Medicine Provider (Physician, nurse, advanced practice provider)	190 (38.5%)	205 (41.5%)	202 (40.8%)
Intensive Care Unit Provider (Physician, nurse, advanced practice provider)	83 (16.8%)	81 (16.4%)	79 (16.0%)
Anesthesia / ENT	105 (21.3%)	90 (18.2%)	88 (17.8%)
First Responder (EMT, paramedic, and others)	65 (13.2%)	58 (11.7%)	57 (11.5%)
Healthcare Worker in Covid-19 Unit	29 (5.9%)	41 (8.3%)	35 (7.1%)
Healthcare Worker in Congregate Care Setting	4 (0.8%)	3 (0.6%)	8 (1.6%)
Other	18 (3.6%)	16 (3.2%)	26 (5.3%)
In what setting do you expect your highest risk exposure could occur? –no. (%)			
Emergency Department	190 (38.5%)	210 (42.5%)	207 (41.8%)
Intensive Care Unit	85 (17.2%)	82 (16.6%)	102 (20.6%)
Clinic	8 (1.6%)	12 (2.4%)	18 (3.6%)
Hospital ward	10 (2.0%)	15 (3.0%)	13 (2.6%)
COVID19 ward	56 (11.3%)	51 (10.3%)	47 (9.5%)
Ambulance, Air Ambulance, Medivac	45 (9.1%)	40 (8.1%)	33 (6.7%)
Operating Room	75 (15.2%)	61 (12.3%)	42 (8.5%)
Congregate Care Setting	20 (4.0%)	19 (3.8%)	27 (5.5%)
Other	5 (1.0%)	1 (0.2%)	5 (1.0%)
Not indicated	0 (0.0%)	3 (0.6%)	1 (0.2%)

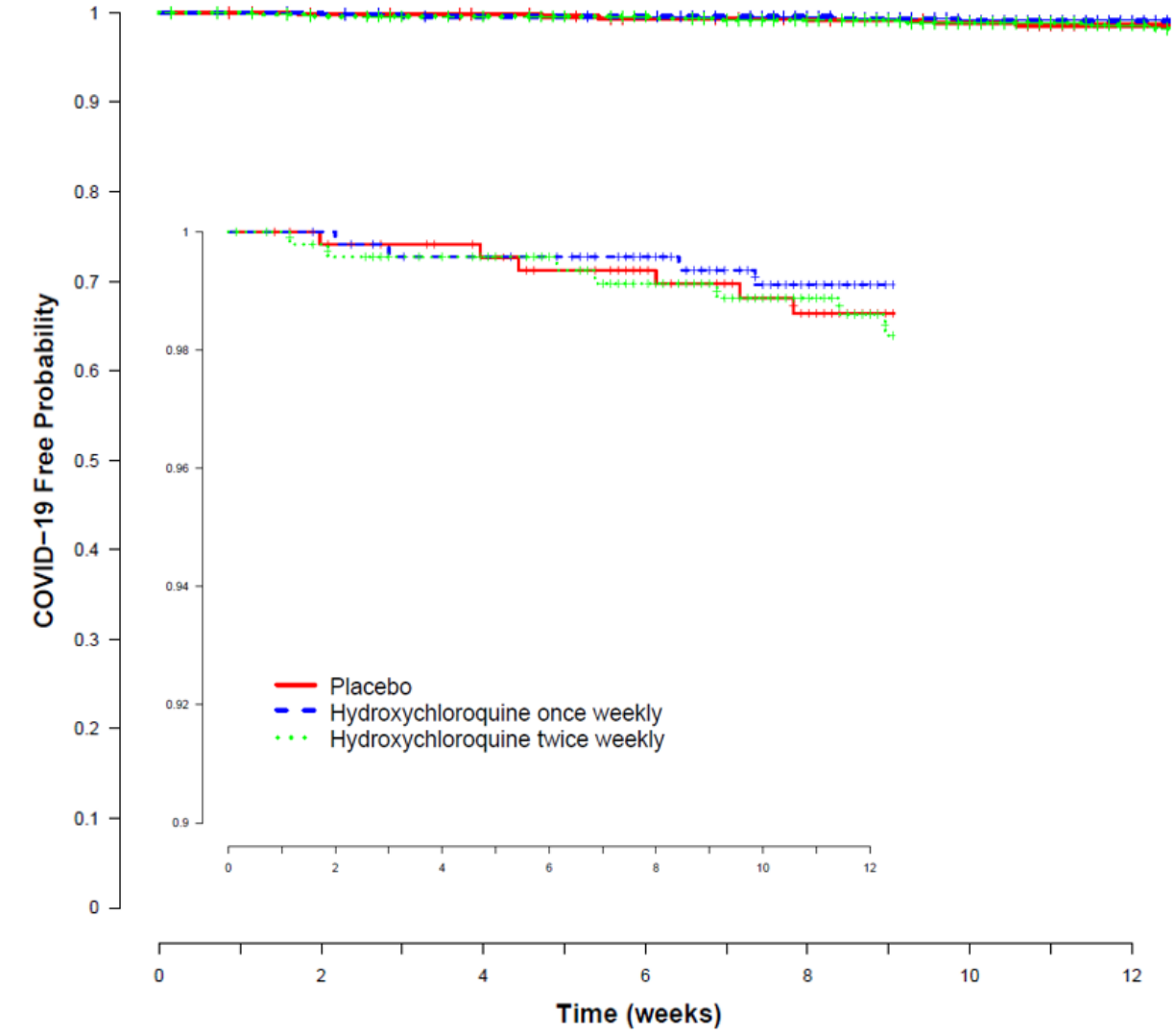
Supplemental Table 3. Primary Event by Symptoms and PCR Testing

	Total (n=1483)	Placebo (n=494)	Hydroxychloroquine once weekly (n=494)	Hydroxychloroquine twice weekly (n=495)
Primary event (confirmed or probable COVID-19)	97 (6.5%)	39 (7.9%)	29 (5.9%)	29 (5.9%)
Positive PCR, symptoms* within 14 days before test	7 (0.5%)	3 (0.6%)	2 (0.4%)	2 (0.4%)
Positive PCR, symptoms* within 14 days after test	9 (0.6%)	2 (0.4%)	2 (0.4%)	5 (1.0%)
Positive PCR, symptoms* earlier than 14 days before test	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Positive PCR, never symptoms	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Probable (Covid-compatible symptoms)**, negative PCR within 4 days before symptoms	30 (2.0%)	16 (3.2%)	10 (2.0%)	4 (0.8%)
Probable (Covid-compatible symptoms)**, negative PCR within 11 days after symptoms	8 (0.5%)	5 (1.0%)	1 (0.2%)	2 (0.4%)
Probable (Covid-compatible symptoms)**, negative PCR beyond 11 days after symptoms	5 (0.3%)	3 (0.6%)	0 (0.0%)	2 (0.4%)
Probable (Covid-compatible symptoms)**, negative PCR earlier than 4 days before symptoms	8 (0.5%)	2 (0.4%)	4 (0.8%)	2 (0.4%)
Probable (Covid-compatible symptoms)**, no test result	29 (2.0%)	7 (1.4%)	10 (2.0%)	12 (2.4%)

* Symptoms are those adjudicated as probably or possibly Covid-19 related. All adjudications were blinded to treatment assignment.

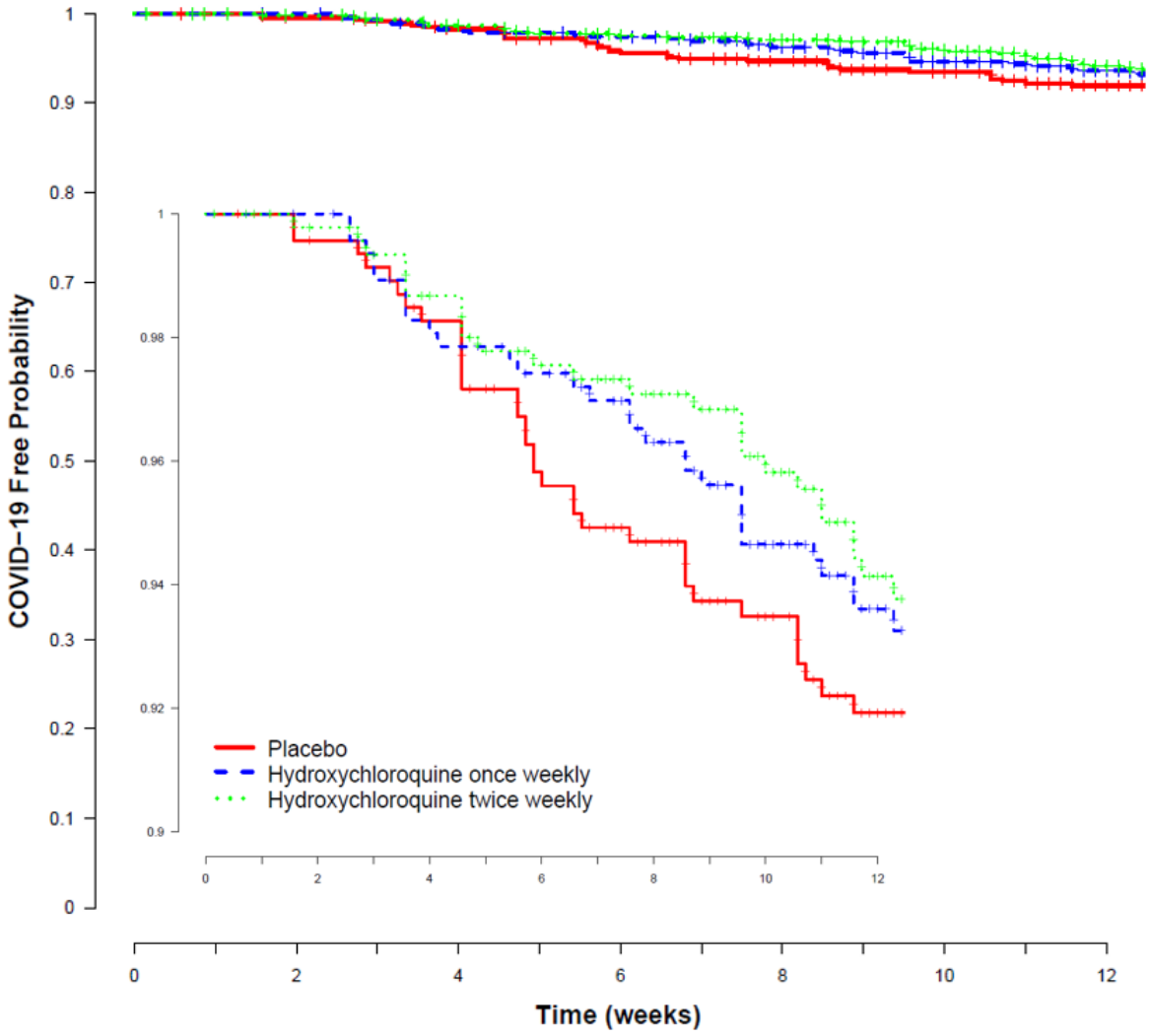
** Probable (Covid-19 compatible symptoms) are those adjudicated as probably Covid-19 related

Figure S3. Kaplan Meier Estimate of Time to Confirmed PCR Positive Covid-19 Infection. The probability of PCR-confirmed Covid-19 infection is shown for the three study groups. The hazard ratio for twice weekly hydroxychloroquine prophylaxis was 1.18 (95%CI 0.40 to 3.51; P=0.77) and for once weekly was 0.65 (95%CI 0.18 to 2.32; P=0.51) as compared with placebo.



No. pts							
Placebo	494	468	462	449	429	396	323
HCQ 1x week	494	474	468	461	442	407	335
HCQ 2x week	495	465	459	442	421	389	316

Figure S4. Kaplan Meier Estimate of Time to Covid-19 Compatible Symptoms. The probability of Covid-19 Compatible symptoms is shown for the three study groups. The hazard ratio for twice weekly hydroxychloroquine prophylaxis was 0.74 (95%CI 0.45 to 1.20; P=0.22) and for once weekly was 0.73 (95%CI 0.45 to 1.19; P=0.21) as compared with placebo.



No. pts							
Placebo	494	461	448	426	402	370	295
HCQ 1x week	494	470	457	447	424	388	315
HCQ 2x week	495	457	443	425	401	371	297

Figure S5. Distribution of Symptoms for Covid-19 Compatible Cases Designated as PCR-Confirmed Covid-19

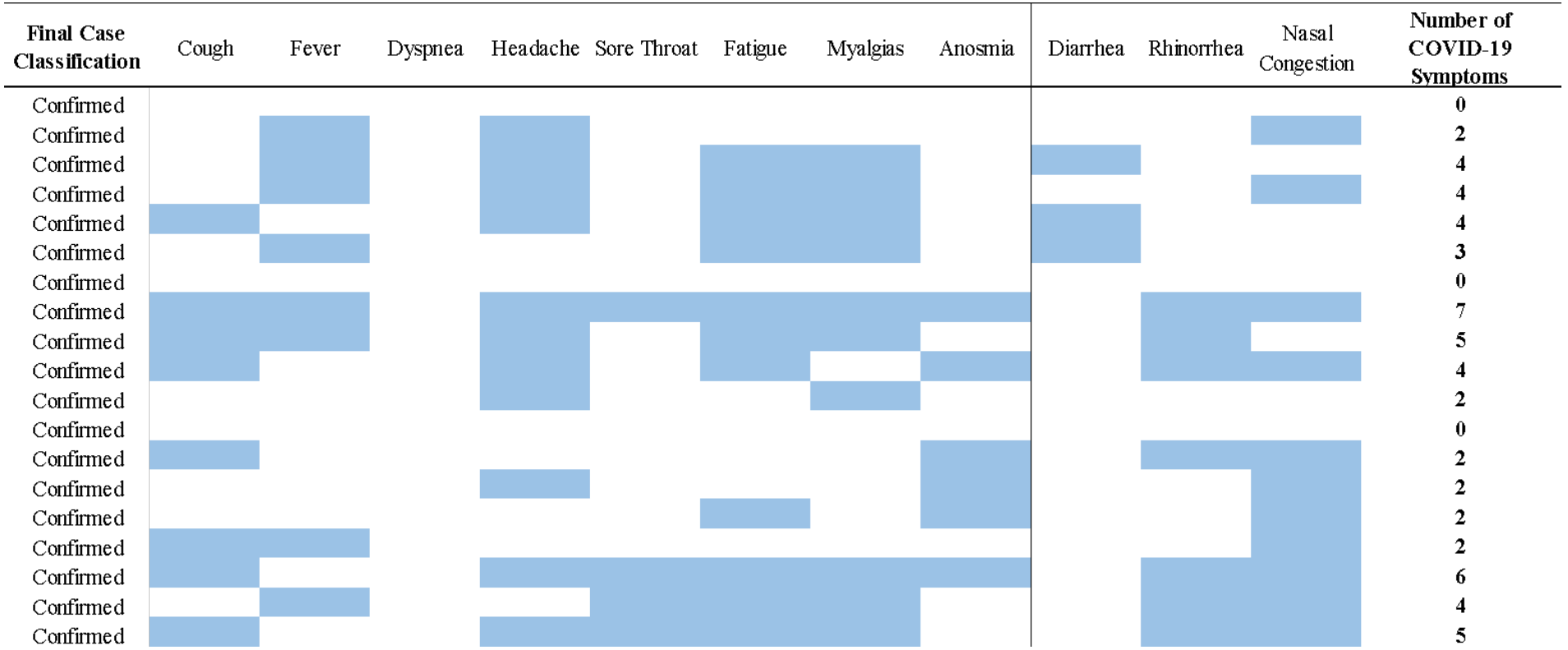
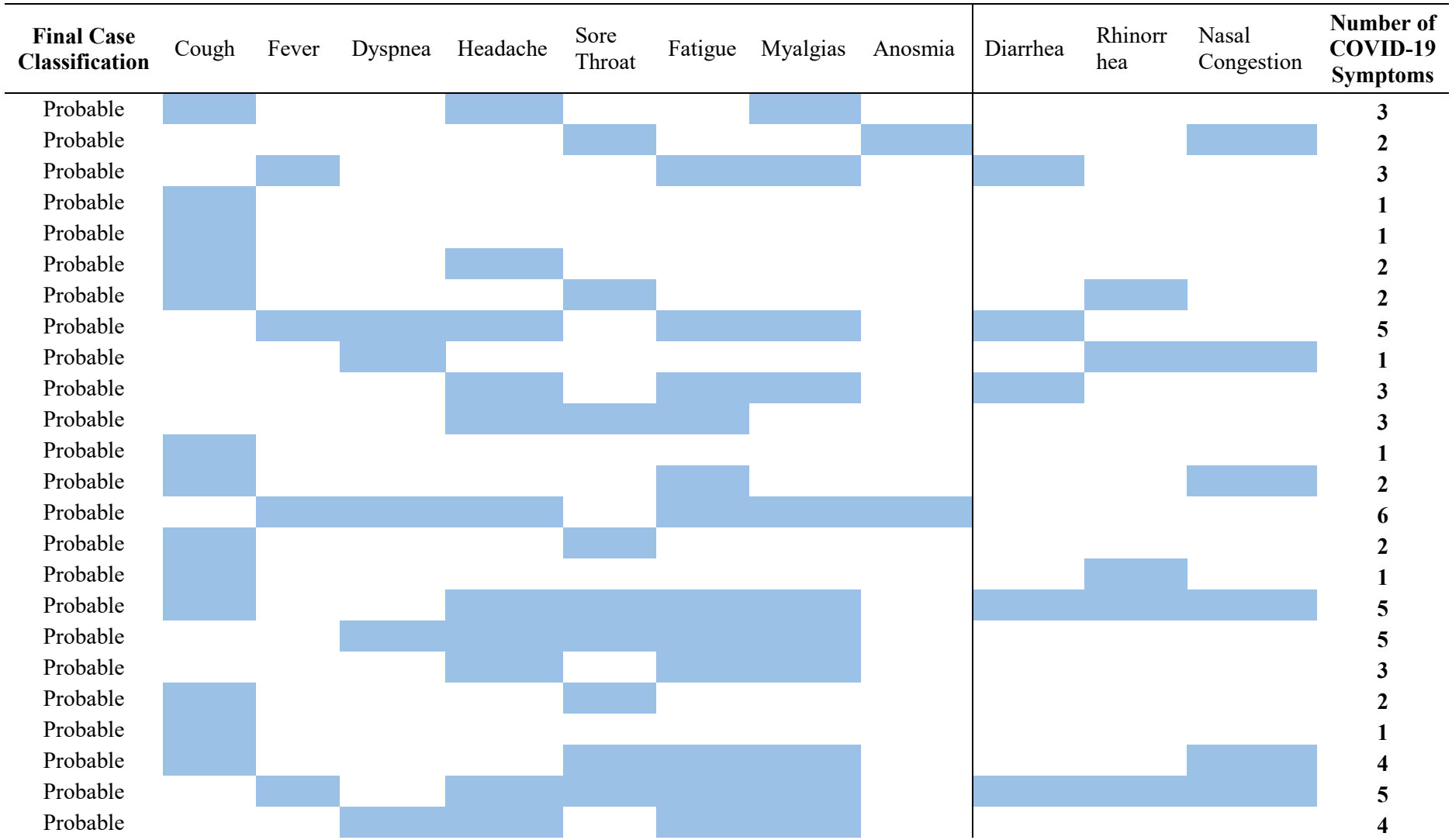


Figure S6. Distribution of Symptoms for Covid-19 Compatible Cases Designated as Probable Covid-19



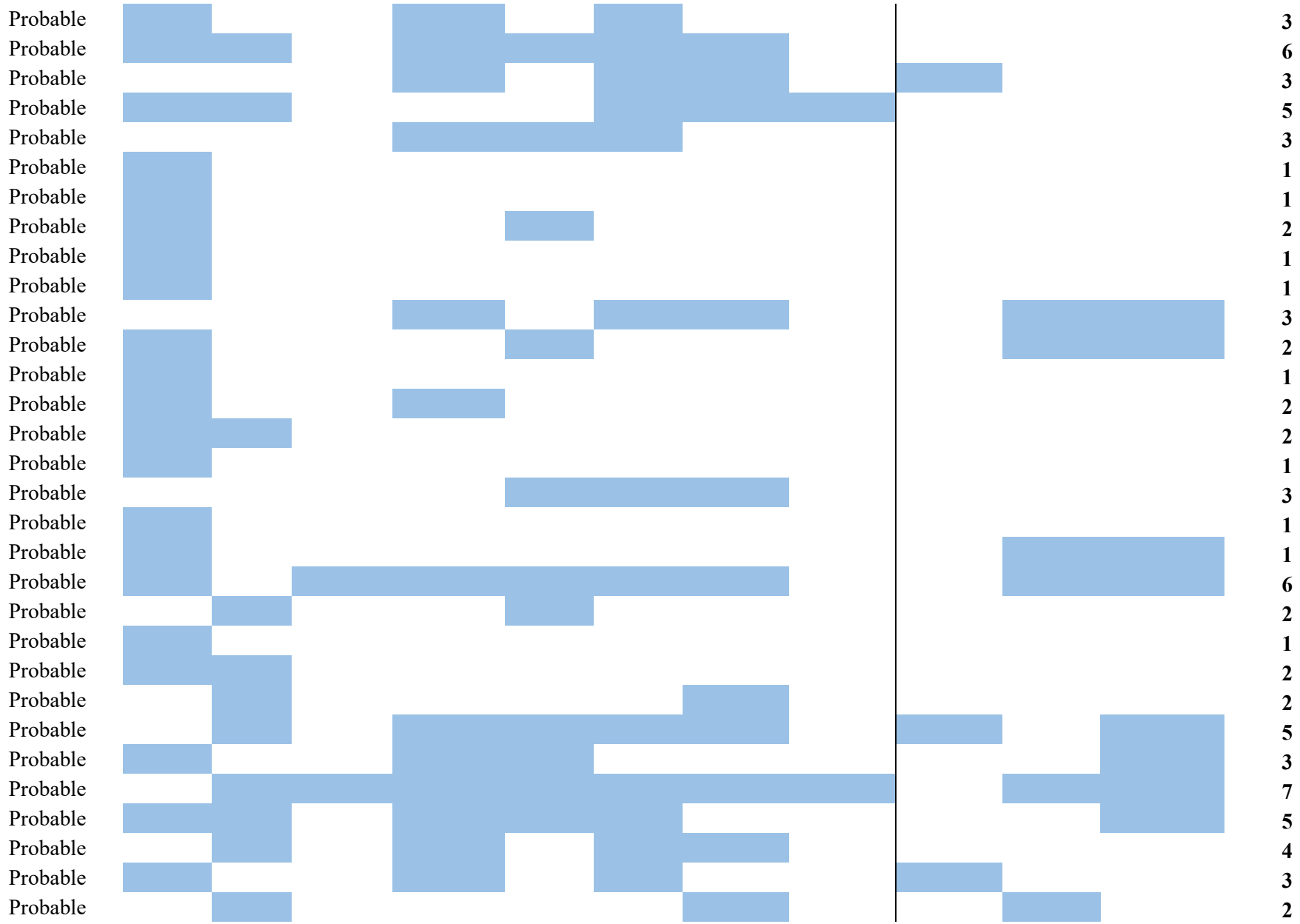

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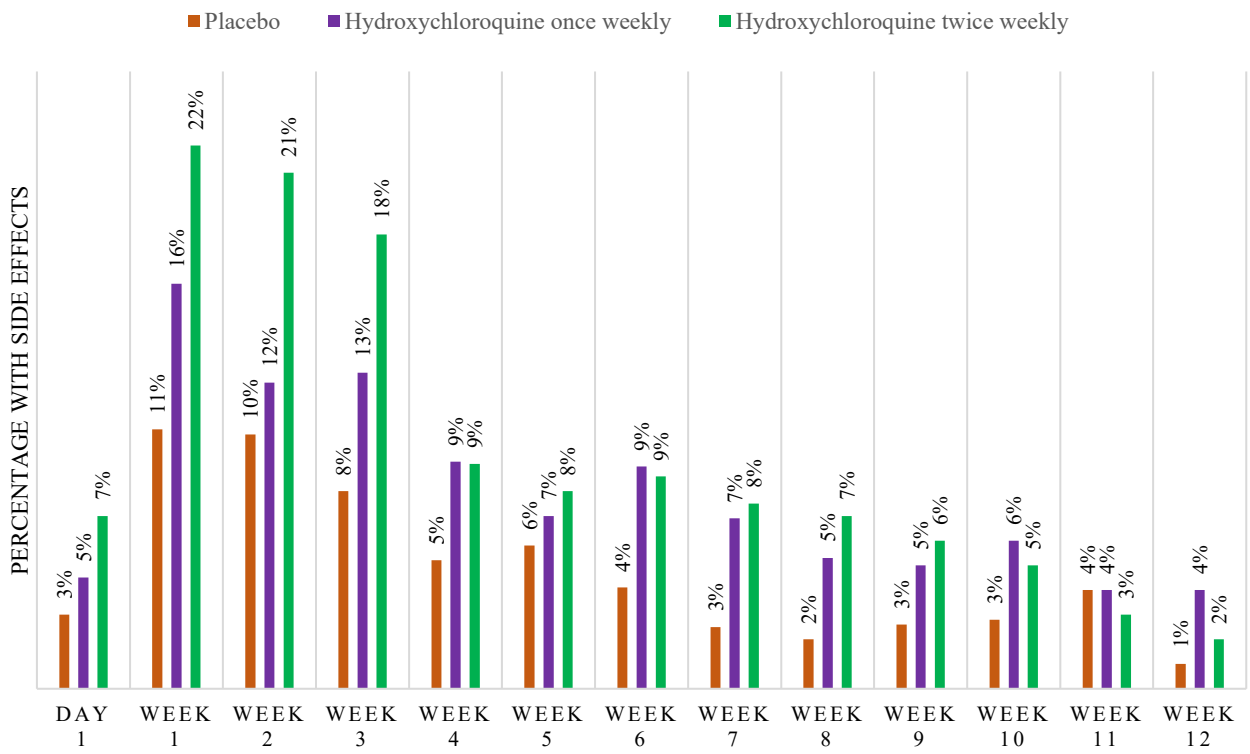
Figure S7. Distribution of Symptoms for Covid-19 Compatible Cases Designated as Possible Covid-19

Inter-observer reliability was 88%. Out of 291 adjudications, 255 were in complete agreement between all three infectious diseases physicians. Rhinorrhea, nasal congestion, and diarrhea are not part of the US case definition (and not included in the count of COVID-related symptoms).

Figure S8. Percentage of Participants Reporting Side Effects From Study Medication, by Week.



Supplemental Table 4. Reported Side Effects Since Starting Study Medicine

	Placebo	Hydroxychloroquine once weekly	Hydroxychloroquine twice weekly
Any side effect, N (%)	100 (21.4%)	148 (31.3%)	168 (36.4%)
Side Effects Present (Not Mutually Exclusive)			
Stomach	57 (12.2%)	83 (17.5%)	90 (19.4%)
Diarrhea/GI	35 (7.5%)	61 (12.9%)	79 (17.1%)
Neurologic	22 (4.7%)	27 (5.7%)	24 (5.2%)
Headache	12 (2.6%)	14 (3.0%)	8 (1.7%)
Skin	11 (2.3%)	13 (2.7%)	23 (5.0%)
Palpitations	8 (1.7%)	4 (0.8%)	6 (1.3%)
Sleep disturbance	7 (1.5%)	10 (2.1%)	7 (1.5%)
Tinnitus	5 (1.1%)	10 (2.1%)	7 (1.5%)
Vision	3 (0.6%)	7 (1.5%)	4 (0.9%)
Allergic Reaction	3 (0.6%)	2 (0.4%)	4 (0.9%)
Myalgia	2 (0.4%)	7 (1.5%)	1 (0.2%)
Bloody nose	1 (0.2%)	1 (0.2%)	1 (0.2%)
Appetite change	1 (0.2%)	2 (0.4%)	1 (0.2%)
Joint pain	1 (0.2%)	3 (0.6%)	0 (0.0%)
Low Energy	1 (0.2%)	1 (0.2%)	5 (1.1%)
Mouth ulcers	0 (0.0%)	1 (0.2%)	4 (0.9%)
Yeast infection	0 (0.0%)	2 (0.4%)	0 (0.0%)
Dry mouth	0 (0.0%)	1 (0.2%)	2 (0.4%)
Other	3 (0.6%)	6 (1.3%)	6 (1.3%)

Each side effect type is counted only once per person

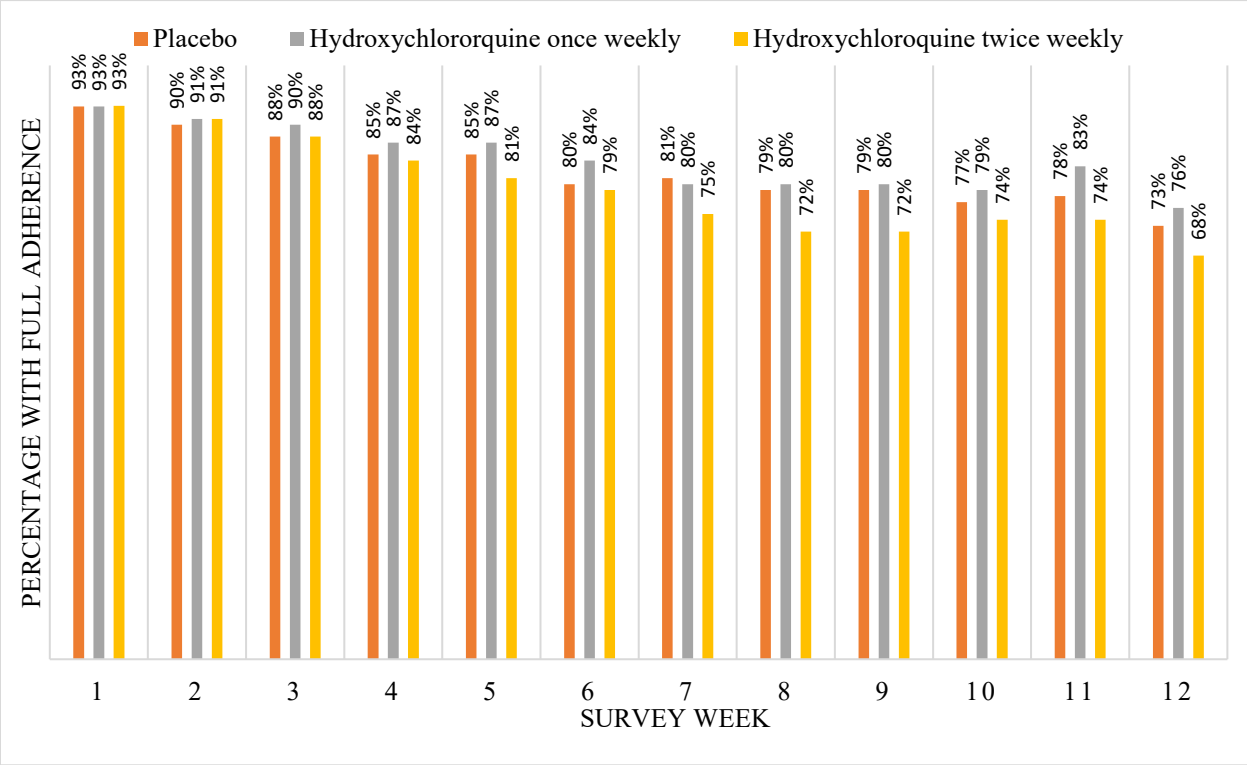
Supplemental Table 5. GI Side Effects (Diarrhea) by Week

	Placebo	Hydroxychloroquine once weekly	Hydroxychloroquine twice weekly
Week 1	13 (3.1%)	23 (5.3%)	39 (9.4%)
Week 2	14 (3.3%)	22 (5.0%)	41 (9.9%)
Week 3	10 (2.4%)	14 (3.2%)	31 (7.5%)
Week 4	9 (2.1%)	12 (2.8%)	16 (3.9%)
Week 5	8 (2.0%)	10 (2.4%)	15 (3.8%)
Week 6	4 (1.0%)	13 (3.1%)	15 (3.9%)
Week 7	2 (0.5%)	10 (2.5%)	14 (3.9%)
Week 8	4 (1.1%)	12 (3.2%)	16 (4.5%)
Week 9	0 (0.0%)	8 (2.3%)	10 (3.1%)
Week 10	1 (0.3%)	7 (2.1%)	6 (2.0%)
Week 11	1 (0.4%)	4 (1.5%)	5 (2.0%)
Week 12	0 (0.0%)	3 (2.0%)	3 (2.3%)

Supplemental Table 6. Stomach Side Effects (Upset Stomach, Nausea) by Week

	Placebo	Hydroxychloroquine once weekly	Hydroxychloroquine twice weekly
Week 1	23 (5.5%)	38 (8.8%)	50 (12.1%)
Week 2	27 (6.3%)	25 (5.7%)	42 (10.1%)
Week 3	18 (4.2%)	27 (6.1%)	38 (9.2%)
Week 4	12 (2.9%)	19 (4.4%)	18 (4.4%)
Week 5	12 (2.9%)	16 (3.8%)	12 (3.0%)
Week 6	11 (2.7%)	18 (4.4%)	12 (3.1%)
Week 7	7 (1.8%)	14 (3.5%)	13 (3.6%)
Week 8	4 (1.1%)	8 (2.1%)	12 (3.4%)
Week 9	7 (2.0%)	9 (2.6%)	10 (3.1%)
Week 10	7 (2.2%)	12 (3.6%)	7 (2.3%)
Week 11	4 (1.6%)	7 (2.6%)	3 (1.2%)
Week 12	1 (0.7%)	5 (3.4%)	1 (0.8%)

Figure S9. Percentage of Participants with Full Medication Adherence by Survey Week

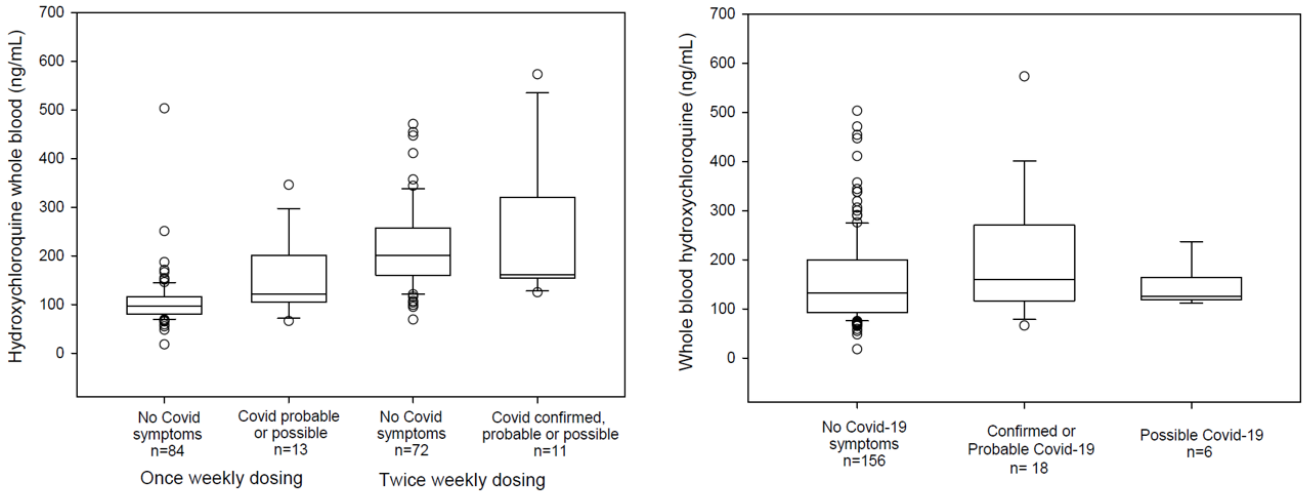


The percentage of participants with full medication adherence by survey week is independent of any other week's adherence (i.e. a non-adherent participant at Week 1 can be counted as adherent at Week 10.)

Supplemental Table 7. Demographics of Participants Enrolled in the Pharmacokinetic Sub-study

	Hydroxychloroquine once weekly (n=97)	Hydroxychloroquine twice weekly (n=83)
Age in years, median (range)	41 (22-68)	43 (23-65)
Female, no. (%)	53 (55)	38 (46)
Weight in kg, median (range)	81.3 (45.0-143.0)	84.0 (52.7-140.7)
Days since drug start at time of sampling, median (range)	35 (27-62)	35 (25-71)
Samples collected >144 hours (once weekly) or >72 hours (twice weekly) post dose, no. (%)	84 (87)	61 (73)

Figure S10. Hydroxychloroquine drug concentrations in whole blood. Left, drug concentrations by dosing. Right, drug concentrations by outcome of confirmed Covid-19, probable Covid-19, possible Covid-19, and no Covid-19.



Supplemental Table 8. Secondary Outcomes

Clinical Outcome	Placebo (n= 494)	Hydroxychloroquine once weekly (n=494)	Hydroxychloroquine twice weekly (n=495)	P value[1]	P value[2]
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Intensive Care Unit admission	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Participants hospitalized	7 (1.4%)	3 (0.6%)	8 (1.6%)	0.34	>0.99
Total number of hospitalizations (SAEs)	9	3	8		
Due to Covid-19	1	0	1		
Due to adverse event	0	0	1		
Due to other reason	8	3	6		
If “other,” specify:	Motor vehicle accident with injury	Hysteroscopy	Elective coronary angiogram		
	Chest pain, palpitations, tachycardia	Diverticulitis	Gallbladder surgery		
	Hyperthyroid, chest pain, palpitations	Spinal surgery	Urinary tract infection		
	Heat related exhaustion and abnormal labs		Outpatient surgery		
	Atrial fibrillation (x2)		Emergent surgery		
	Kidney stone, urinary tract infection		Other, not specified (x2)		
	Sarcoidosis related skin biopsy				

All p-values are Fishers Exact or Wilcoxon Rank Sum. P value[1] for Hydroxychloroquine once weekly vs placebo, P value[2] for Hydroxychloroquine twice weekly vs placebo.

Supplemental Table 9. Combined Hydroxychloroquine Arms Compared to Placebo

	Placebo (n=494)	**Hydroxychloroquine (n=989)**	**HR (95% CI)**	**P Value**
PCR positive or probable Covid-19	39 (7.9%)	58 (5.9%)	0.73 (0.48 to 1.09)	0.12

Supplemental Table 10. Subgroup Analysis of Risk of Covid-19 Compatible Illness with Hydroxychloroquine Once Weekly

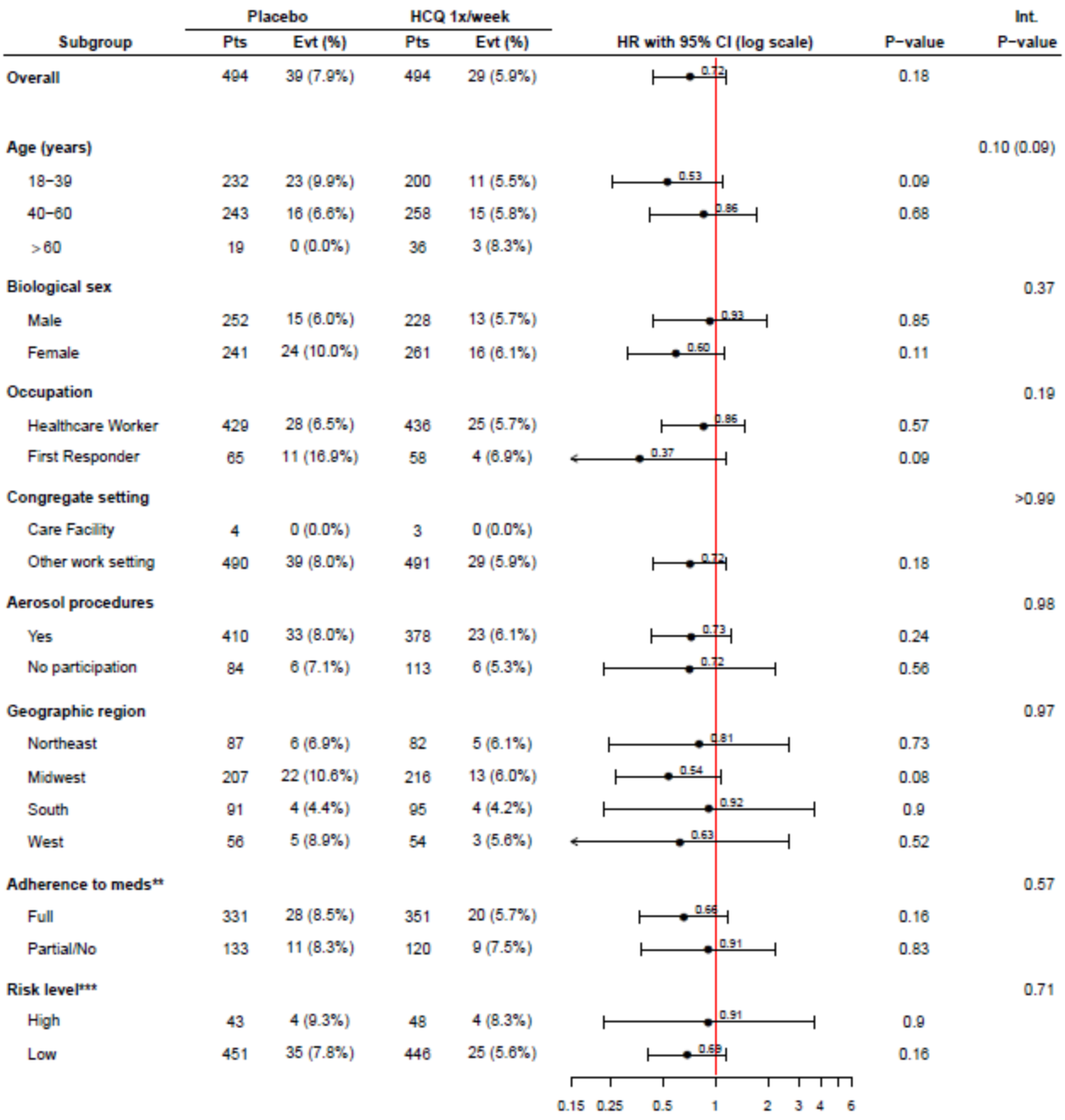
	Placebo			Hydroxychloroquine once weekly					
	No. People	**Events N (%)**	**Rate per Person Year**	**No. People**	**Events N (%)**	**Rate per Person Year**	**HR (95% CI)**	**Subgroup P-value**	**Interaction P-value**
Overall N	494			494					
Age, years									0.10
18-39	232	23 (9.9%)	0.50 (0.29, 0.70)	200	11 (5.5%)	0.27 (0.11, 0.42)	0.53 (0.26, 1.09)	0.09	
40-60	243	16 (6.6%)	0.31 (0.16, 0.46)	258	15 (5.8%)	0.27 (0.13, 0.40)	0.86 (0.43, 1.74)	0.68	
>60	19	0 (0.0%)	0.00 (0.00, 0.00)	36	3 (8.3%)	0.38 (0.00, 0.81)			
Interaction p-value from continuous model									0.09
Biologic Sex									0.37
Male	252	15 (6.0%)	0.28 (0.14, 0.42)	228	13 (5.7%)	0.26 (0.12, 0.40)	0.93 (0.44, 1.96)	0.85	
Female	241	24 (10.0%)	0.50 (0.30, 0.70)	261	16 (6.1%)	0.30 (0.15, 0.44)	0.60 (0.32, 1.12)	0.11	
Occupation									0.19
Healthcare Worker	429	28 (6.5%)	0.31 (0.20, 0.43)	436	25 (5.7%)	0.27 (0.16, 0.37)	0.86 (0.50, 1.47)	0.57	
First Responder	65	11 (16.9%)	0.88 (0.36, 1.41)	58	4 (6.9%)	0.33 (0.01, 0.65)	0.37 (0.12, 1.17)	0.09	
Setting									>0.99
Congregate Care Facility	4	0 (0.0%)	0.00 (0.00, 0.00)	3	0 (0.0%)	0.00 (0.00, 0.00)			
Any other	490	39 (8.0%)	0.38 (0.26, 0.50)	491	29 (5.9%)	0.28 (0.18, 0.38)	0.72 (0.44, 1.16)	0.18	

Aerosol-generating procedures								0.98
Yes	410	33 (8.0%)	0.39 (0.26, 0.52)	378	23 (6.1%)	0.28 (0.17, 0.40)	0.73 (0.43, 1.24)	0.24
No	84	6 (7.1%)	0.35 (0.07, 0.63)	113	6 (5.3%)	0.25 (0.05, 0.45)	0.72 (0.23, 2.22)	0.56
Overall study-drug adherence [x]								0.57
Adherent at 80% of surveys	331	28 (8.5%)	0.38 (0.24, 0.53)	351	20 (5.7%)	0.25 (0.14, 0.36)	0.66 (0.37, 1.17)	0.16
Adherent <80% of surveys	133	11 (8.3%)	0.40 (0.16, 0.63)	120	9 (7.5%)	0.35 (0.12, 0.58)	0.91 (0.38, 2.20)	0.83
Risk Level [y]								0.71
High	43	4 (9.3%)	0.46 (0.01, 0.92)	48	4 (8.3%)	0.43 (0.01, 0.85)	0.91 (0.23, 3.66)	0.90
Low	451	35 (7.8%)	0.37 (0.25, 0.50)	446	25 (5.6%)	0.26 (0.16, 0.36)	0.69 (0.41, 1.16)	0.16
Geographic Region								0.97
Northeast	87	6 (6.9%)	0.34 (0.07, 0.62)	82	5 (6.1%)	0.28 (0.03, 0.53)	0.81 (0.25, 2.65)	0.73
Midwest	207	22 (10.6%)	0.50 (0.29, 0.71)	216	13 (6.0%)	0.27 (0.12, 0.42)	0.54 (0.27, 1.07)	0.08
South	91	4 (4.4%)	0.22 (0.00, 0.44)	95	4 (4.2%)	0.20 (0.00, 0.40)	0.92 (0.23, 3.67)	0.90
West	56	5 (8.9%)	0.43 (0.05, 0.80)	54	3 (5.6%)	0.27 (0.00, 0.57)	0.63 (0.15, 2.62)	0.52

[x] Among those with any adherence data. Note that this is NOT a baseline subgroup. Credit was given for partial adherence to account for the twice weekly group.

[y] High risk if no N95 or PAPR OR no eye protection with > 14 patient-facing hours AND performing aerosol-generating procedures

Figure S11. Forest Plot of *A priori* Identified Subgroups, Hydroxychloroquine Once Weekly



** Among those with any adherence data. NOTE this is NOT a baseline subgroup. Credit was given for partial adherence to account for the twice weekly group

*** High risk if no N95 or PAPR OR no eye protection with >14 pt−facing hours, AND performing aerosol−generating procedures

Supplemental Table 11. Subgroup Analysis of Risk of Covid-19 Compatible Illness with Hydroxychloroquine Twice Weekly

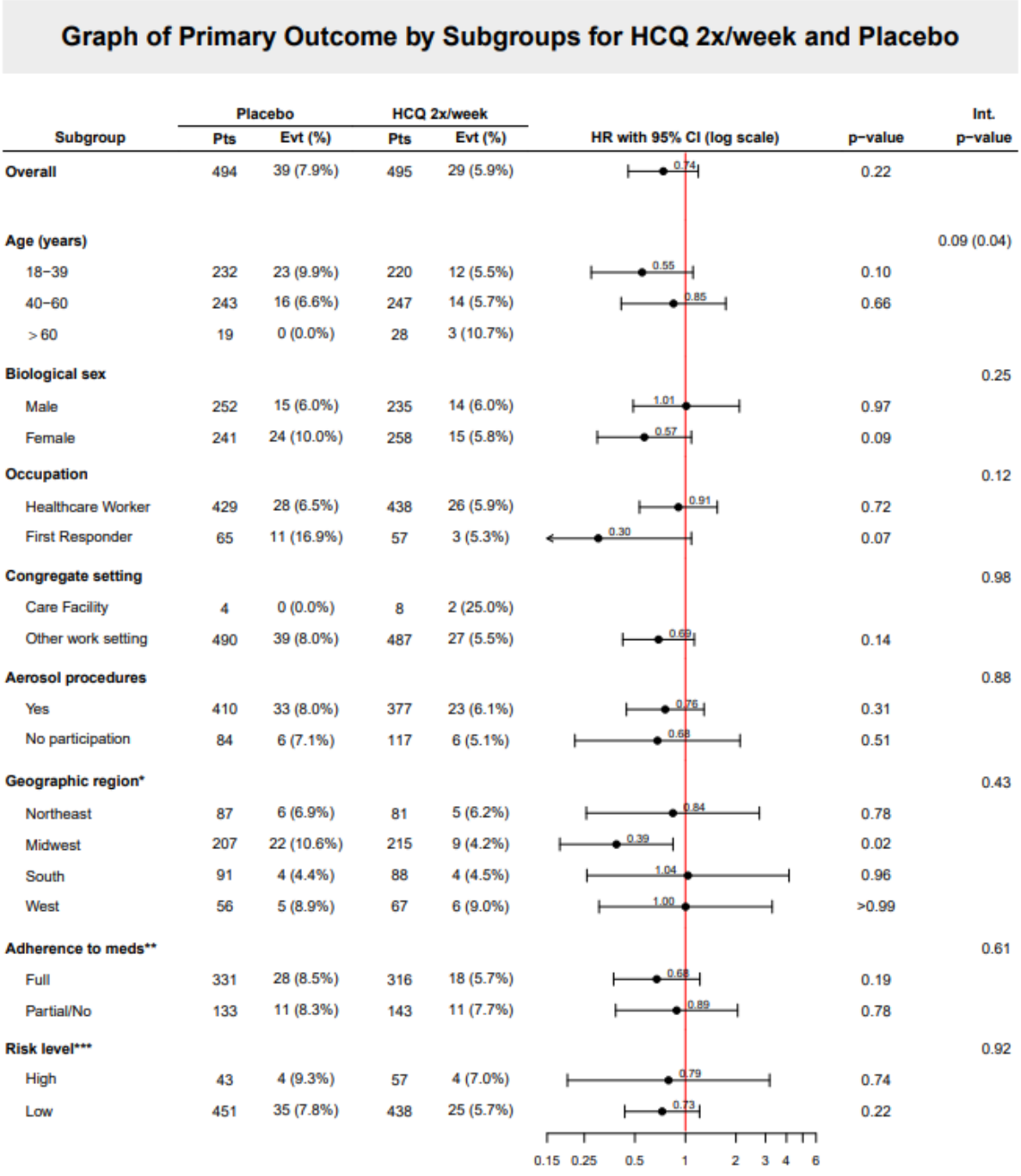
	Placebo			Hydroxychloroquine twice weekly					
	No. People	**Events N (%)**	**Rate per Person Year**	**No. People**	**Events N (%)**	**Rate per Person Year**	**HR (95% CI)**	**Subgroup P-value**	**Interaction P-value**
Overall N	494		495						
Age, years									0.09
18-39	232	23 (9.9%)	0.50 (0.29, 0.70)	220	12 (5.5%)	0.28 (0.12, 0.43)	0.55 (0.27, 1.11)	0.10	
40-60	243	16 (6.6%)	0.31 (0.16, 0.46)	247	14 (5.7%)	0.26 (0.12, 0.40)	0.85 (0.41, 1.74)	0.66	
>60	19	0 (0.0%)	0.00 (0.00, 0.00)	28	3 (10.7%)	0.51 (0.00, 1.08)			
Interaction p-value from continuous model									0.04
Biologic Sex									0.25
Male	252	15 (6.0%)	0.28 (0.14, 0.42)	235	14 (6.0%)	0.28 (0.13, 0.43)	1.01 (0.49, 2.10)	0.97	
Female	241	24 (10.0%)	0.50 (0.30, 0.70)	258	15 (5.8%)	0.28 (0.14, 0.43)	0.57 (0.30, 1.09)	0.09	
Occupation									0.12
Healthcare Worker	429	28 (6.5%)	0.31 (0.20, 0.43)	438	26 (5.9%)	0.28 (0.17, 0.39)	0.91 (0.53, 1.55)	0.72	
First Responder	65	11 (16.9%)	0.88 (0.36, 1.41)	57	3 (5.3%)	0.27 (0.00, 0.57)	0.30 (0.08, 1.09)	0.07	
Setting									0.98
Congregate Care Facility	4	0 (0.0%)	0.00 (0.00, 0.00)	8	2 (25.0%)	1.50 (0.00, 3.58)			
Any other	490	39 (8.0%)	0.38 (0.26, 0.50)	487	27 (5.5%)	0.27 (0.17, 0.37)	0.69 (0.42, 1.13)	0.14	
Aerosol-generating procedures									0.88
Yes	410	33 (8.0%)	0.39 (0.26, 0.52)	377	23 (6.1%)	0.29 (0.17, 0.42)	0.76 (0.45, 1.29)	0.31	
No	84	6 (7.1%)	0.35 (0.07, 0.63)	117	6 (5.1%)	0.24 (0.05, 0.44)	0.68 (0.22, 2.12)	0.51	

Overall study-drug adherence [x]									0.61
Adherent at 80% of surveys submitted	331	28 (8.5%)	0.38 (0.24, 0.53)	316	18 (5.7%)	0.26 (0.14, 0.38)	0.68 (0.37, 1.22)	0.19	
Adherent at less than 80% of surveys submitted	133	11 (8.3%)	0.40 (0.16, 0.63)	143	11 (7.7%)	0.35 (0.14, 0.56)	0.89 (0.38, 2.05)	0.78	
Risk Level [y]									0.92
High	43	4 (9.3%)	0.46 (0.01, 0.92)	57	4 (7.0%)	0.36 (0.01, 0.72)	0.79 (0.20, 3.17)	0.71	
Low	451	35 (7.8%)	0.37 (0.25, 0.50)	438	25 (5.7%)	0.27 (0.17, 0.38)	0.73 (0.44, 1.21)	0.22	
Geographic Region									0.43
Northeast	87	6 (6.9%)	0.34 (0.07, 0.62)	81	5 (6.2%)	0.29 (0.04, 0.55)	0.84 (0.26, 2.76)	0.78	
Midwest	207	22 (10.6%)	0.50 (0.29, 0.71)	215	9 (4.2%)	0.20 (0.07, 0.33)	0.39 (0.18, 0.84)	0.02	
South	91	4 (4.4%)	0.22 (0.00, 0.44)	88	4 (4.5%)	0.23 (0.00, 0.46)	1.04 (0.26, 4.14)	0.96	
West	56	5 (8.9%)	0.43 (0.05, 0.80)	67	6 (9.0%)	0.42 (0.08, 0.75)	1.00 (0.31, 3.29)	>0.99	

[x] Among those with any adherence data. Note that this is NOT a baseline subgroup. Credit was given for partial adherence to account for the twice weekly group

[y] High risk if no N95 or PAPR OR no eye protection with > 14 patient-facing hours, AND performing aerosol-generating procedures

Figure S12. Forest Plot of *A priori* Identified Subgroups, Hydroxychloroquine Twice Weekly



Sensitivity Analyses

1. Include participants who had confirmed or probable Covid-19 onset after randomization but before study medication was initiated

	Placebo (n=498)	Hydroxychloroquine once weekly (n=498)	HR[1]	P Value[1]	Hydroxychloroquine twice weekly (n=500)	HR[2]	P Value[2]
PCR positive or probable Covid-19 or possible Covid-19	40 (8.0%)	29 (5.8%)	0.70 (0.43 to 1.12)	0.14	30 (6.0%)	0.74 (0.46 to 1.19)	0.22

[1] Comparing hydroxychloroquine once weekly to placebo [2] Comparing hydroxychloroquine twice weekly to placebo

2. Exclude participants who had confirmed or probable Covid-19 onset after randomization but before the first weekly survey was completed

	Placebo (n=492)	Hydroxychloroquine once weekly (n=492)	HR[1]	P Value[1]	Hydroxychloroquine twice weekly (n=493)	HR[2]	P Value[2]
PCR positive or probable Covid-19 or possible Covid-19	37 (7.5%)	27 (5.5%)	0.70 (0.43 to 1.16)	0.17	27 (5.5%)	0.72 (0.44 to 1.19)	0.20

[1] Comparing hydroxychloroquine once weekly to placebo [2] Comparing hydroxychloroquine twice weekly to placebo

3. Primary event includes confirmed Covid-19, probable Covid-19, and possible Covid-19 (based on symptoms)

	Placebo (n=494)	Hydroxychloroquine once weekly (n=494)	HR[1]	P Value[1]	Hydroxychloroquine twice weekly (n=495)	HR[2]	P Value[2]
PCR positive or probable Covid-19 or possible Covid-19	49 (9.9%)	40 (8.1%)	0.78 (0.52 to 1.19)	0.25	40 (8.1%)	0.80 (0.53 to 1.22)	0.31

[1] Comparing hydroxychloroquine once weekly to placebo [2] Comparing hydroxychloroquine twice weekly to placebo

4. Exclude participants who were protocol violations

	Placebo (n=493)	Hydroxychloroquine once weekly (n=490)	HR[1]	P Value[1]	Hydroxychloroquine twice weekly (n=493)	HR[2]	P Value[2]
PCR positive or probable Covid-19 or possible Covid-19	39 (7.9%)	29 (5.9%)	0.72 (0.45 to 1.17)	0.18	29 (5.9%)	0.74 (0.46 to 1.20)	0.22

[1] Comparing hydroxychloroquine once weekly to placebo [2] Comparing hydroxychloroquine twice weekly to placebo

5. Exclude events in participants who had PCR negative testing despite Covid-19 compatible symptoms

	Placebo (n=494)	Hydroxychloroquine once weekly (n=494)	HR[1]	P Value[1]	Hydroxychloroquine twice weekly (n=496)	HR[2]	P Value[2]
PCR positive or probable Covid-19 (without negative PCR testing)	15 (3.0%)	14 (2.8%)	0.90 (0.43 to 1.86)	0.78	20 (4.0%)	1.32 (0.67 to 2.57)	0.42

[1] Comparing hydroxychloroquine once weekly to placebo [2] Comparing hydroxychloroquine twice weekly to placebo

6. Exclude participants who had confirmed or probable Covid-19 before the fourth weekly survey was completed (after which steady state levels would be achieved)

	Placebo (n=477)	Hydroxychloroquine once weekly (n=479)	HR[1]	P Value[1]	Hydroxychloroquine twice weekly (n=476)	HR[2]	P Value[2]
PCR positive or probable Covid-19 (without negative PCR testing)	26 (5.5%)	18 (3.8%)	0.66 (0.36 to 1.21)	0.18	18 (3.8%)	0.69 (0.38 to 1.26)	0.23

[1] Comparing hydroxychloroquine once weekly to placebo [2] Comparing hydroxychloroquine twice weekly to placebo

Supplemental Table 12. Participant Guess of Study Arm at Completion of Study

	Placebo	**Hydroxychloroquine once weekly**	**Hydroxychloroquine twice weekly**
N answered question	417	425	405
Guessed hydroxychloroquine	65 (15.6%)	176 (41.4%)	141 (34.8%)
Guessed placebo	156 (37.4%)	54 (12.7%)	61 (15.1%)
Not sure	196 (47.0%)	195 (45.9%)	203 (50.1%)

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