ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For persons who are exposed, the standard of care is observation and quarantine. Whether hydroxychloroquine can prevent symptomatic infection after SARS-CoV-2 exposure is unknown.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial across the United States and parts of Canada testing hydroxychloroquine as postexposure prophylaxis. We enrolled adults who had household or occupational exposure to someone with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure). Within 4 days after exposure, we randomly assigned participants to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days). The primary outcome was the incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days.

RESULTS

We enrolled 821 asymptomatic participants. Overall, 87.6% of the participants (719 of 821) reported a high-risk exposure to a confirmed Covid-19 contact. The incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was –2.4 percentage points (95% confidence interval, –7.0 to 2.2; P=0.35). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

CONCLUSIONS

After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure. (Funded by David Baszucki and Jan Ellison Baszucki and others; ClinicalTrials.gov number, NCT04308668.)

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the global, rapidly emerging virus causing coronavirus disease 2019 (Covid-19).[1] The current public health strategies to mitigate transmission are rapid identification of cases, isolation, contact tracing, and self-quarantine of those exposed. Once a person is exposed, observation and quarantine during a 14-day incubation period is the standard of care. To date, no medication has been shown to prevent SARS-CoV-2 transmission.

Both chloroquine and the derivative molecule hydroxychloroquine have in vitro activity against SARS-CoV and SARS-CoV-2.[2,3] Hydroxychloroquine is thought to impair the terminal glycosylation of the angiotensin-converting–enzyme 2 (ACE2) receptor, which is the binding site for the envelope spike glycoprotein and has been shown to inhibit endolysosome function.[2,4] In addition, hydroxychloroquine may have greater in vitro activity against SARS-CoV-2 than chloroquine.[3]

The majority of clinical studies of chloroquine or hydroxychloroquine for Covid-19 have focused on hospitalized patients.[5-8] Yet, to alter the trajectory of the epidemic, it is necessary to break the chain of transmission. The risk of secondary household transmission has been estimated as 10 to 15%.[9,10] Small, nonrandomized, noncontrolled cohort studies have suggested that the use of hydroxychloroquine might reduce or even eliminate this risk.[11] Whether short-term high-dose hydroxychloroquine can prevent disease soon after a high-risk exposure remains unknown. We hypothesized that hydroxychloroquine could potentially be used as postexposure prophylaxis, to prevent symptomatic infection after exposure to Covid-19.

Methods

Trial Design and Oversight

We conducted a randomized, double-blind, placebo-controlled trial to evaluate postexposure prophylaxis with hydroxychloroquine after exposure to Covid-19.[12] We randomly assigned participants in a 1:1 ratio to receive either hydroxychloroquine or placebo. Participants had known exposure (by participant report) to a person with laboratory-confirmed Covid-19, whether as a household contact, a health care worker, or a person with other occupational exposures.

Trial enrollment began on March 17, 2020, with an eligibility threshold to enroll within 3 days after exposure; the objective was to intervene before the median incubation period of 5 to 6 days. Because of limited access to prompt testing, health care workers could initially be enrolled on the basis of presumptive high-risk exposure to patients with pending tests; however, on March 23, eligibility was changed to exposure to a person with a positive polymerase-chain-reaction (PCR) assay for SARS-CoV-2, with the eligibility window extended to within 4 days after exposure.

This trial was approved by the institutional review board at the University of Minnesota and conducted under a Food and Drug Administration Investigational New Drug application. In Canada, the trial was approved by Health Canada; ethics approvals were obtained from the Research Institute of the McGill University Health Centre, the University of Manitoba, and the University of Alberta.

Participants

We included participants who had household or occupational exposure to a person with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure). Participants were excluded if they were younger than 18 years of age, were hospitalized, or met other exclusion criteria (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Persons with symptoms of Covid-19 or with PCR-proven SARS-CoV-2 infection were excluded from this prevention trial but were separately enrolled in a companion clinical trial to treat early infection.

Setting

Recruitment was performed primarily with the use of social media outreach as well as traditional media platforms. Participants were enrolled nationwide in the United States and in the Canadian provinces of Quebec, Manitoba, and Alberta. Participants enrolled themselves through a secure Internet-based survey using the Research Electronic Data Capture (REDCap) system.[13] After participants read the consent form, their comprehension of its contents was assessed; participants provided a digitally captured signature to indicate informed consent. We sent follow-up e-mail surveys on days 1, 5, 10, and 14. A survey at 4 to

6 weeks asked about any follow-up testing, illness, or hospitalizations. Participants who did not respond to follow-up surveys received text messages, e-mails, telephone calls, or a combination of these to ascertain their outcomes. When these methods were unsuccessful, the emergency contact provided by the enrollee was contacted to determine the participant's illness and vital status. When all communication methods were exhausted, Internet searches for obituaries were performed to ascertain vital status.

INTERVENTIONS

Randomization occurred at research pharmacies in Minneapolis and Montreal. The trial statisticians generated a permuted-block randomization sequence using variably sized blocks of 2, 4, or 8, with stratification according to country. A research pharmacist sequentially assigned participants. The assignments were concealed from investigators and participants; only pharmacies had access to the randomization sequence.

Hydroxychloroquine sulfate or placebo was dispensed and shipped overnight to participants by commercial courier. The dosing regimen for hydroxychloroquine was 800 mg (4 tablets) once, then 600 mg (3 tablets) 6 to 8 hours later, then 600 mg (3 tablets) daily for 4 more days for a total course of 5 days (19 tablets total). If participants had gastrointestinal upset, they were advised to divide the daily dose into two or three doses. We chose this hydroxychloroquine dosing regimen on the basis of pharmacokinetic simulations to achieve plasma concentrations above the SARS-CoV-2 in vitro half maximal effective concentration for 14 days.[14] Placebo folate tablets, which were similar in appearance to the hydroxychloroquine tablets, were prescribed as an identical regimen for the control group. Rising Pharmaceuticals provided a donation of hydroxychloroquine, and some hydroxychloroquine was purchased.

OUTCOMES

The primary outcome was prespecified as symptomatic illness confirmed by a positive molecular assay or, if testing was unavailable, Covid-19–related symptoms. We assumed that health care workers would have access to Covid-19 testing if symptomatic; however, access to testing was limited throughout the trial period. Covid-19–related symptoms were based on U.S. Council for State and Territorial Epidemiologists criteria for confirmed cases (positivity for SARS-Cov-2 on PCR assay), probable cases (the presence of cough, shortness of breath, or difficulty breathing, or the presence of two or more symptoms of fever, chills, rigors, myalgia, headache, sore throat, and new olfactory and taste disorders), and possible cases (the presence of one or more compatible symptoms, which could include diarrhea).[15] All the participants had epidemiologic linkage,[15] per trial eligibility criteria. Four infectious disease physicians who were unaware of the trial-group assignments reviewed symptomatic participants to generate a consensus with respect to whether their condition met the case definition.[15]

Secondary outcomes included the incidence of hospitalization for Covid-19 or death, the incidence of PCR-confirmed SARS-CoV-2 infection, the incidence of Covid-19 symptoms, the incidence of discontinuation of the trial intervention owing to any cause, and the severity of symptoms (if any) at days 5 and 14 according to a visual analogue scale (scores ranged from 0 [no symptoms] to 10 [severe symptoms]). Data on adverse events were also collected with directed questioning for common side effects along with open-ended free text. Outcome data were measured within 14 days after trial enrollment. Outcome data including PCR testing results, possible Covid-19–related symptoms, adherence to the trial intervention, side effects, and hospitalizations were all collected through participant report. Details of trial conduct are provided in the protocol and statistical analysis plan, available at NEJM.org.

SAMPLE SIZE

We anticipated that illness compatible with Covid-19 would develop in 10% of close contacts exposed to Covid-19.[9] Using Fisher's exact method with a 50% relative effect size to reduce new symptomatic infections, a two-sided alpha of 0.05, and 90% power, we estimated that 621 persons would need to be enrolled in each group. With a pragmatic, Internet-based, self-referral recruitment strategy, we planned for a 20% incidence of attrition by increasing the sample size to 750 participants per group. We specified a priori that participants who were already symptomatic on day 1 before receiving hydroxychloroquine or placebo would be excluded from the prophylaxis trial and would instead be separately enrolled in the companion symptomatic treatment trial.

Because the estimates for both incident symptomatic Covid-19 after an exposure and loss to follow-up were relatively unknown in early March 2020,[9] the protocol prespecified a sample-size reestimation at the second interim analysis. This reestimation, which used the incidence of new infections in the placebo group and the observed percentage of participants lost to follow-up, was aimed at maintaining the ability to detect an effect size of a 50% relative reduction in new symptomatic infections.

INTERIM ANALYSES

An independent data and safety monitoring board externally reviewed the data after 25% and 50% of the participants had completed 14 days of follow-up. Stopping guidelines were provided to the data and safety monitoring board with the use of a Lan–DeMets spending function analogue of the O'Brien–Fleming boundaries for the primary outcome. A conditional power analysis was performed at the second and third interim analysis with the option of early stopping for futility. At the second interim analysis on April 22, 2020, the sample size was reduced to 956 participants who could be evaluated with 90% power on the basis of the higher-than-expected event rate of infections in the control group. At the third interim analysis on May 6, the trial was halted on the basis of a conditional power of less than 1%, since it was deemed futile to continue.

STATISTICAL ANALYSIS

We assessed the incidence of Covid-19 disease by day 14 with Fisher's exact test. Secondary outcomes with respect to percentage of patients were also compared with Fisher's exact test. Among participants in whom incident illness compatible with Covid-19 developed, we summarized the symptom severity score at day 14 with the median and interquartile range and assessed the distributions with a Kruskal–Wallis test. We conducted all analyses with SAS software, version 9.4 (SAS Institute), according to the intention-to-treat principle, with two-sided type I error with an alpha of 0.05. For participants with missing outcome data, we conducted a sensitivity analysis with their outcomes excluded or included as an event. Subgroups that were specified a priori included type of contact (household vs. health care), days from exposure to enrollment, age, and sex.

RESULTS

PARTICIPANTS

We recruited 821 asymptomatic adult participants who were randomly assigned to the hydroxychloroquine group (414 participants) or the placebo group (407 participants) (Fig. 1). The demographic and clinical characteristics of the participants are provided in Table 1. The median age was 40 years (interquartile range, 33 to 50). Women accounted for 51.6% of the trial participants (424 of 821). A total of 27.4% of the participants (225 of 821) reported chronic health conditions, with hypertension being the most common (99 of 821 [12.1%]), followed by asthma (62 of 821 [7.6%]). Health care workers accounted for 66.4% of the participants (545 of 821), the majority being physicians or physician assistants (342 of 545 [62.8%]) and nurses or nursing assistants (128 of 545 [23.5%]). In the case of health care workers, exposure was predominantly from patients (418 of 545 [76.7%]) or ill coworkers (107 of 545 [19.6%]). Among the 29.8% of the participants (245 of 821) who enrolled as a household contact, the majority reported that their Covid-19 contact exposure was either a spouse or partner (114 of 245 [46.5%]) or a parent (43 of 245 [17.6%]).

Overall, 87.6% of the participants (719 of 821) had high-risk exposures without eye shields and surgical masks or respirators. Of those, 365 received hydroxychloroquine and 354 received placebo. Approximately 60% of the participants reported not wearing any element of personal protective equipment during their Covid-19 exposure.

PRIMARY OUTCOME

Overall, new Covid-19 (either PCR-confirmed or symptomatically compatible) developed in 107 of 821 participants (13.0%) during the 14 days of follow-up (Table 2). The incidence of new illness compatible with Covid-19 did not differ significantly between those receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]) ($P=0.35$). The absolute difference was –2.4 percentage points (95% confidence interval, –7.0 to 2.2). Figure 2 shows the development of Covid-19 over time. Two hospitalizations were reported (one in each group). No arrhythmias or deaths occurred. There was no meaningful difference in effectiveness according

to the time of starting postexposure prophylaxis or in any of the prespecified subgroups (Fig. S1 in the Supplementary Appendix). Overall, 10.7% of the participants (46 in the hydroxychloroquine group and 42 in the placebo group) did not complete the day 14 survey; among these participants, vital status was unknown for 36 in the hydroxychloroquine group and 33 in the control group. In sensitivity analyses, exclusion of these persons from the denominator or inclusion of them as having had an event did not affect the trial conclusions (Table S1).

Of 113 persons in whom symptomatic illness developed, 16 had PCR-confirmed disease, 74 had illness that was compatible with probable Covid-19 per the U.S. case definition, 13 had possible Covid-19 with compatible symptoms and epidemiologic linkage, and 10 were adjudicated as not having Covid-19 on the basis of the symptom complex (Table S2). Four additional participants had positive PCR tests and were asymptomatic during the 14-day trial period; symptoms eventually developed in 3 of these participants. The median number of symptoms was 4 (interquartile range, 2 to 5) among participants with Covid-19. The most frequent symptoms were cough (44.9% of the 107 participants with Covid-19), fever (34.6%), shortness of breath (18.7%), fatigue (49.5%), sore throat (40.2%), myalgia (37.4%), and anosmia (23.4%). Among participants who were symptomatic at day 14, the median symptom-severity score (on a scale from 0 to 10, with higher scores indicating greater severity) was 2.8 (interquartile range, 1.6 to 5.0) in those receiving hydroxychloroquine and 2.7 (interquartile range, 1.4 to 4.8) in those receiving placebo (P=0.34).

ADHERENCE AND SAFETY

Adherence among the trial participants was moderate. Full adherence to the trial intervention differed according to trial group, with 75.4% of participants in the hydroxychloroquine group (312 of 414) and 82.6% of those in the placebo group (336 of 407) having taken all 19 prescribed tablets over a period of 5 days (P=0.01). The most common reason that participants stopped taking the assigned hydroxychloroquine or placebo was side effects (17 participants in the hydroxychloroquine group and 8 in the placebo group). Side effects were more frequent with hydroxychloroquine than with placebo (Table 3). Among the

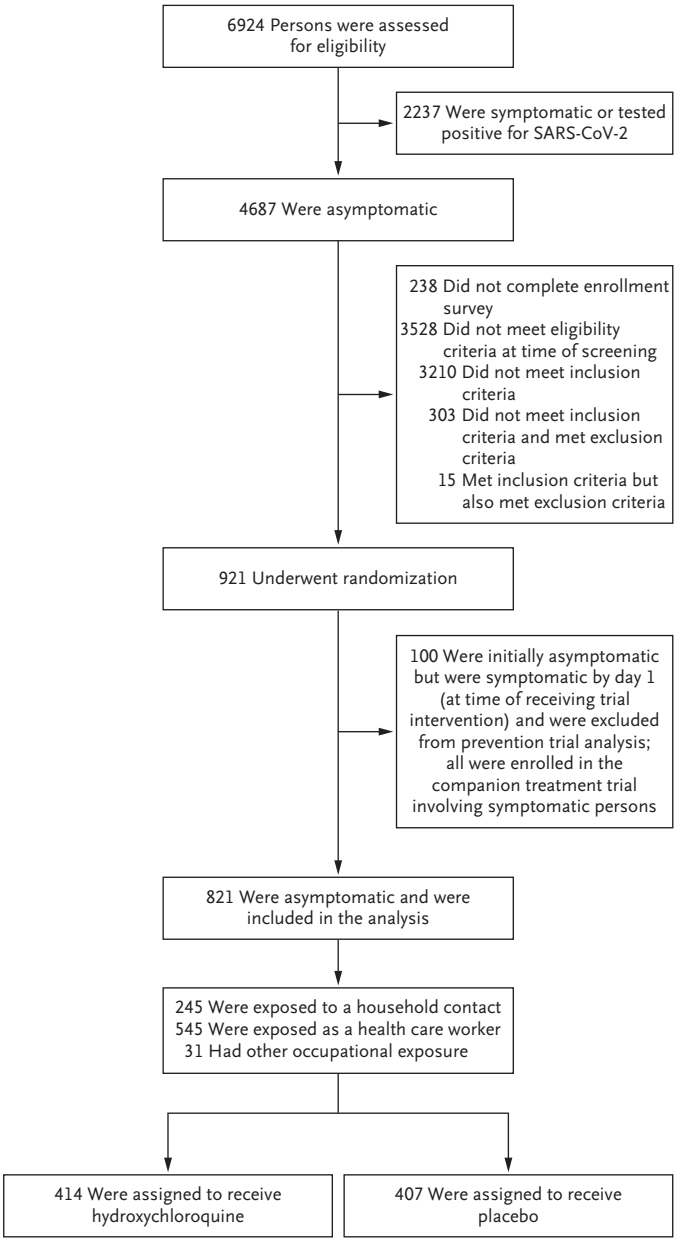

Figure 1. Screening and Randomization.

Of the 821 participants who underwent randomization, 96 did not complete the day 14 follow-up survey, of whom 8 formally withdrew from the trial (4 in each group). Investigators confirmed the vital status and lack of infection in 19 participants (10 in the hydroxychloroquine group and 9 in the control group); 17 completed some follow-up surveys without symptoms before being lost to follow-up (13 in the hydroxychloroquine group and 4 in the control group). A total of 52 participants never completed any surveys after enrollment and did not respond to investigators e-mails, text messages, or telephone calls (23 in the hydroxychloroquine group and 29 in the control group). SARS-CoV-2 denotes severe acute respiratory syndrome coronavirus 2.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Hydroxychloroquine (N=414)	Placebo (N=407)
Median age (IQR) — yr	41 (33–51)	40 (32–50)
Median weight (IQR) — kg	75 (64–86)	76 (64–91)
Female sex — no. (%)†	218 (52.7)	206 (50.6)
Current smoker — no. (%)	15 (3.6)	12 (2.9)
Health care worker — no. (%)	275 (66.4)	270 (66.3)
High-risk exposure — no. (%)‡	365 (88.2)	354 (87.0)
No PPE worn — no. (%)	258 (62.3)	237 (58.2)
Time from exposure to enrollment — no./total no. (%)		
1 day	77/413 (18.6)	63/407 (15.5)
2 days	100/413 (24.2)	106/407 (26.0)
3 days	98/413 (23.7)	117/407 (28.7)
4 days	138/413 (33.4)	121/407 (29.7)
Coexisting conditions — no. (%)		
None	306 (73.9)	290 (71.3)
Hypertension	51 (12.3)	48 (11.8)
Asthma	31 (7.5)	31 (7.6)
Diabetes	12 (2.9)	16 (3.9)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range, and PPE personal protective equipment.
† A total of 0.2% of the women (1 of 424) were pregnant and 1.4% (6 of 424) were breast-feeding at the time of enrollment. One woman (0.2%) reported new pregnancy at day 14.
‡ High-risk exposure was defined as exposure to a person with confirmed coronavirus disease 2019 (Covid-19) at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield.

participants who took any hydroxychloroquine, 40.1% (140 of 349) reported a side effect by day 5, as compared with 16.8% (59 of 351) receiving placebo (P<0.001). Nausea, loose stools, and abdominal discomfort were the most common side effects. There were no serious intervention-related adverse reactions or cardiac arrhythmias.

On day 14, we assessed how well the masking of the trial interventions was maintained. Of the 344 participants in the hydroxychloroquine group who completed the day 14 survey question, 160 (46.5%) correctly identified that they received hydroxychloroquine, 151 (43.9%) were unsure, and 33 (10%) believed that they received placebo. Of the 353 participants in the control group who completed the day 14 survey question, 126 (35.7%) correctly identified that they received placebo, 168 (47.6%) were unsure, and 59 (16.7%) believed that they received hydroxychloroquine. Participants who reported any side effect (regardless of trial group) at day 5 were 3.7 times as likely to believe that they received hydroxychloroquine as participants who did not report side effects (122 of 179 participants [68.2%] reporting side effects and 94 of 504 participants [18.7%] not reporting side effects; P<0.001). In the absence of side effects, blinding was well maintained.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, we investigated the efficacy of hydroxychloroquine as Covid-19 postexposure

Table 2. Outcomes of Hydroxychloroquine Therapy for Postexposure Prophylaxis against Covid-19.*

Outcome	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
	number (percent)		
Confirmed or probable Covid-19	49 (11.8)	58 (14.3)	0.35
Laboratory-confirmed diagnosis	11 (2.7)	9 (2.2)	0.82
Symptoms compatible with Covid-19	48 (11.6)	55 (13.5)	0.46
All new symptoms	57 (13.8)	59 (14.5)	0.84
Any hospitalization	1 (0.2)	1 (0.2)	0.99
Death	0	0	—

* Symptoms were adjudicated by four infectious disease physicians, who were unaware of the trial-group assignments, in accordance with U.S. Council of State and Territorial Epidemiologists case definition of probable Covid-19 after an epidemiologic link with a close contact.[15] (Descriptions of the symptom complex are provided in the Supplementary Appendix.) The median number of new symptoms reported in the hydroxychloroquine group was 4 (interquartile range, 2 to 6), as compared with 3 (interquartile range, 2 to 5) in the placebo group.

prophylaxis. In this trial, high doses of hydroxychloroquine did not prevent illness compatible with Covid-19 when initiated within 4 days after a high-risk or moderate-risk exposure.

We used a pragmatic approach to recruitment and follow-up of participants through Internet-based self-referral and online follow-up surveys, and we couriered the trial interventions directly to participants' homes. This approach allowed for recruitment across North America, minimized the risk of SARS-CoV-2 infection to researchers, lowered the burden of research participation, and provided a timely answer to this question of whether postexposure prophylaxis was effective. Moreover, this approach allowed broad geographic participation regardless of anyone's physical distance from academic centers, increasing the generalizability of the findings. One result of our approach was that enrolled participants were generally younger and healthier than those at risk for severe Covid-19. Although the risk of severe Covid-19 is related to age and coexisting conditions,[16] the risk of acquiring symptomatic infection is generally still present among adults, regardless of age. Although PCR or serologic testing for asymptomatic infection would have added to the scientific strength of this trial, this was not possible, and we cannot assess an effect on mild or asymptomatic infections. Although a marginal possible benefit from prophylaxis in a more at-risk group cannot be ruled out, the potential risks that are associated with hydroxychloroquine may also be increased in more at-risk populations, and this may essentially negate any benefits that were not shown in this large trial involving younger, healthier participants.

We acknowledge that this trial has limitations. Because of the lack of availability of diagnostic testing in the United States, the vast majority of the participants, including health care workers, were unable to access testing. Thus, an a priori symptomatic case definition was used — the U.S. clinical case definition of probable Covid-19.[15] This trial represents real-world implementation after exposure. In the context of a randomized trial design, any non–SARS-CoV-2 viral infection (e.g., influenza, adenovirus, or rhinovirus) should be equally distributed in the trial groups. Owing to the Internet-based approach used to rapidly recruit participants in the context of a pandemic, data were obtained by means of participant report. The types and frequency of symptoms that were observed are similar to those in previous studies involving U.S. health care providers.[17] The U.S. case definition is how probable Covid-19 cases are nationally reportable.[15,18] However, the predictive power of this case definition is unknown, particularly in the younger populations that we studied; given the small number of PCR tests, it remains theoretically possible that hydroxychloroquine therapy limits proven infection. Reproduction of our results in other, ongoing trials would confirm our findings.

This randomized trial did not demonstrate a significant benefit of hydroxychloroquine as postexposure prophylaxis for Covid-19. Whether pre-

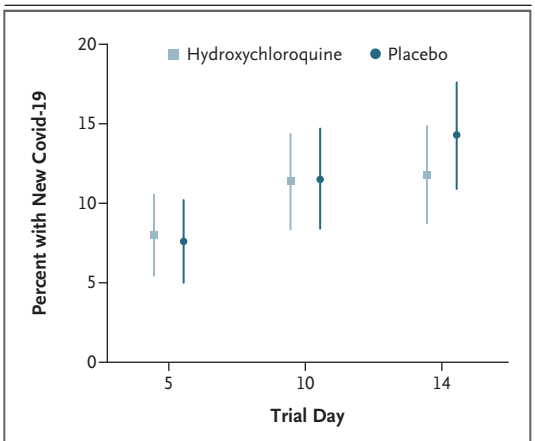

Figure 2. Cumulative Incidence of Illness Compatible with Coronavirus Disease (Covid-19).

The cumulative incidence of illness compatible with Covid-19 was 11.8% in the hydroxychloroquine group (49 of 414 participants) and 14.3% in the placebo group (58 of 407) (P=0.35). The difference equates to a number needed to treat to prevent one infection of 42 persons (lower boundary of the 95% confidence interval for the number needed to treat to prevent one infection, 14 persons; upper boundary of the 95% confidence interval for the number needed to treat to harm 1 person, 50 persons). When we excluded participants who were lost to follow-up, who withdrew, or who were not fully adherent to the trial intervention, the results were similar. When we excluded 13 persons with possible Covid-19 cases who had only one symptom compatible with Covid-19 and no laboratory confirmation, the incidence of new Covid-19 still did not differ significantly between the two groups: 10.4% in the hydroxychloroquine group (43 of 414 participants) and 12.5% in the placebo group (51 of 407) (P=0.38). The vertical bars represent 95% confidence intervals. (Details on symptoms and the adjudication of cases are provided in the Supplementary Appendix.)

Table 3. Participant-Reported Adherence and Side Effects.*

Variable	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
Reported taking any assigned hydroxychloroquine or placebo — no. (%)	349 (84.3)	351 (86.2)	
Reported 100% adherence to trial intervention — no. (%)	312 (75.4)	336 (82.6)	0.01
Reasons that participants did not take all the assigned hydroxychloroquine or placebo — no. (%)			
Side effects	17 (4.1)	8 (2.0)	
Advised to not take hydroxychloroquine	6 (1.4)	2 (0.5)	
Intervention not received from courier	9 (2.2)	2 (0.5)	
Took nontrial hydroxychloroquine	4 (1.0)	0	
Felt no longer at risk	5 (1.2)	3 (0.7)	
Other reason	12 (2.9)	10 (2.5)	
Side effects in participants who started trial intervention — no./total no. (%)			
Any	140/349 (40.1)	59/351 (16.8)	<0.001
Nausea or upset stomach	80/349 (22.9)	27/351 (7.7)	
Diarrhea, abdominal discomfort, or vomiting	81/349 (23.2)	15/351 (4.3)	
Neurologic reaction: irritability, dizziness, or vertigo	19/349 (5.4)	13/351 (3.7)	
Headache	13/349 (3.7)	8/351 (2.3)	
Tinnitus	8/349 (2.3)	3/351 (0.9)	
Visual changes	3/349 (0.9)	0/351	
Skin reaction	4/349 (1.1)	2/351 (0.6)	
Allergic reaction	1/349 (0.3)	1/351 (0.3)	
Fatigue	1/349 (0.3)	1/351 (0.3)	
Taste change or dry mouth	3/349 (0.9)	2/351 (0.6)	
Hot flashes, night sweats, or palpitations	0/349	1/351 (0.3)	

* Values are through day 5, the date of the scheduled completion of the trial intervention. More than one side effect could occur. Ongoing side effects were reported by approximately 3% of the participants in the hydroxychloroquine group at days 10 and 14 and by less than 1% of those in the placebo group. There was no association between the occurrence of side effects and the incidence of Covid-19. Among participants in whom Covid-19 developed, 30.0% (30 of 100) reported a side effect, as compared with 28.2% (169 of 600) reporting a side effect in whom Covid-19 did not develop (P=0.72).

exposure prophylaxis would be effective in high-risk populations is a separate question, with trials ongoing. In order to end the pandemic, a reduction in community transmission is needed.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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