ORIGINAL ARTICLE

A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19

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ABSTRACT

BACKGROUND

Current strategies for preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are limited to nonpharmacologic interventions. Hydroxychloroquine has been proposed as a postexposure therapy to prevent coronavirus disease 2019 (Covid-19), but definitive evidence is lacking.

METHODS

We conducted an open-label, cluster-randomized trial involving asymptomatic contacts of patients with polymerase-chain-reaction (PCR)–confirmed Covid-19 in Catalonia, Spain. We randomly assigned clusters of contacts to the hydroxychloroquine group (which received the drug at a dose of 800 mg once, followed by 400 mg daily for 6 days) or to the usual-care group (which received no specific therapy). The primary outcome was PCR-confirmed, symptomatic Covid-19 within 14 days. The secondary outcome was SARS-CoV-2 infection, defined by symptoms compatible with Covid-19 or a positive PCR test regardless of symptoms. Adverse events were assessed for up to 28 days.

RESULTS

The analysis included 2314 healthy contacts of 672 index case patients with Covid-19 who were identified between March 17 and April 28, 2020. A total of 1116 contacts were randomly assigned to receive hydroxychloroquine and 1198 to receive usual care. Results were similar in the hydroxychloroquine and usual-care groups with respect to the incidence of PCR-confirmed, symptomatic Covid-19 (5.7% and 6.2%, respectively; risk ratio, 0.86 [95% confidence interval, 0.52 to 1.42]). In addition, hydroxychloroquine was not associated with a lower incidence of SARS-CoV-2 transmission than usual care (18.7% and 17.8%, respectively). The incidence of adverse events was higher in the hydroxychloroquine group than in the usual-care group (56.1% vs. 5.9%), but no treatment-related serious adverse events were reported.

CONCLUSIONS

Postexposure therapy with hydroxychloroquine did not prevent SARS-CoV-2 infection or symptomatic Covid-19 in healthy persons exposed to a PCR-positive case patient. (Funded by the crowdfunding campaign YoMeCorono and others; BCN-PEP-CoV2 ClinicalTrials.gov number, NCT04304053.)

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This article was published on November 24, 2020, at NEJM.org.

N Engl J Med 2021;384:417-27.
DOI: 10.1056/NEJMoa2021801

Coronavirus disease 2019 (Covid-19) is a rapidly emerging infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Among contacts of persons with Covid-19, the percentage in whom new cases develop (secondary attack rate) has been estimated at 10 to 15%.[1-4] The current infection-control strategy is based on nonpharmacologic interventions, including hand hygiene, use of face masks, social distancing, and isolation of case patients and contacts.[5] The effectiveness of isolation depends on the promptness of the intervention, the level of contact tracing, and the level of isolation adherence.[6] Unfortunately, real-world constraints for implementing full effective measures have resulted in the spread of SARS-CoV-2 in many countries.

Postexposure prophylaxis of healthy contacts is among the measures used for outbreak control of several infectious diseases (e.g., pandemic influenza).[7] No agent is known to be effective in preventing SARS-CoV-2 infection or Covid-19, but two aminoquinolines — hydroxychloroquine and chloroquine — are among the drugs that have shown antiviral activity in the laboratory.[8] In vitro results showed that these drugs blocked SARS-CoV-2 viral spread in cell cultures[9-11] and that hydroxychloroquine was more effective at impairing SARS-CoV-2 viral replication than chloroquine.[11] The results of one randomized, controlled trial of hydroxychloroquine for postexposure prophylaxis of Covid-19 have been reported.[12] However, concerns have been raised about the trial design. Of the participants with confirmed or probable Covid-19 (primary outcome), fewer than 20% had a positive polymerase-chain-reaction (PCR) test for SARS-COV-2; the rest received a diagnosis on the basis of symptoms alone.

In the Barcelona Postexposure Prophylaxis Study against SARS-CoV-2 (BCN-PEP-CoV2), we investigated the efficacy and safety of hydroxychloroquine to prevent secondary PCR-confirmed, symptomatic Covid-19 and SARS-CoV-2 infection in contacts exposed to a PCR-positive case patient with Covid-19 during the early stages of the outbreak in Catalonia, the region with the second highest number of Covid-19 cases in Spain. (Even when not specified, symptomatic Covid-19 hereafter refers to PCR-confirmed, symptomatic Covid-19.)

Methods

Participants

We included asymptomatic adults (≥18 years of age) who had a recent history of close-contact exposure to a PCR-confirmed case patient with Covid-19 (i.e., >15 minutes within 2 m, up to 7 days before enrollment), who had no Covid-19–like symptoms during the 2 weeks before enrollment, and who had an increased risk of infection (e.g., a health care worker, a household contact, a nursing-home worker, or a nursing-home resident). Trial candidates were tested by PCR assay for SARS-CoV-2 infection at baseline. We included candidates with either a negative or positive PCR test at baseline to assess the prophylactic and preemptive effect of hydroxychloroquine treatment, respectively. All eligibility criteria are listed in the Supplementary Appendix and the trial protocol, both available with the full text of this article at NEJM.org.

Trial Design and Oversight

This was an open-label, phase 3, cluster-randomized trial conducted from March 17 to April 28, 2020, during the early stages of the Covid-19 outbreak, in three of nine health administrative regions in Catalonia, Spain (total target population, 4,206,440) (Fig. S1 in the Supplementary Appendix). Trial candidates were screened with the use of the electronic registry of the national health information system.[13]

The trial was supported by the crowdfunding campaign YoMeCorono (https://www.yomecorono.com/), Generalitat de Catalunya, Zurich Seguros, Synlab Diagnósticos, Laboratorios Rubió, and Laboratorios Gebro Pharma. Laboratorios Rubió donated and supplied the hydroxychloroquine (Dolquine). The sponsors had no role in the conduct of the trial, the analysis, or the decision to submit the manuscript for publication. The trial protocol and subsequent amendments were approved by the institutional review board at Hospital Germans Trias i Pujol and the Spanish Agency of Medicines and Medical Devices. All the participants provided written informed consent.

Trial Procedures

We defined trial clusters (called rings) of healthy persons (contacts) who were epidemiologically linked to a PCR-positive case patient with Covid-19

(index case patient). All the contacts in a ring simultaneously underwent cluster randomization (in a 1:1 ratio) to either the hydroxychloroquine group or the usual-care group. Contacts in the former group received hydroxychloroquine (Dolquine) at a dose of 800 mg on day 1, followed by 400 mg once daily for 6 days; the dosing regimen was based on pharmacokinetic simulations. Contacts in the usual-care group received no specific therapy. After cluster randomization, we verified the selection criteria of individual candidates, obtained informed consent, and revealed the trial-group assignments. In accordance with national guidelines, all the contacts were quarantined.

All the contacts were visited at home or in the workplace on day 1 (enrollment) and day 14 (final outcome measurement) for assessment of health status and collection of nasopharyngeal swabs. Symptoms were monitored by telephone on days 3 and 7. Contacts in whom symptoms developed at any time point were visited at home within 24 hours for assessment of health status and collection of nasopharyngeal swabs. Safety (i.e., frequency and severity of adverse events), medication adherence (i.e., treatment and number of doses taken), and crossover (i.e., unplanned conversion from usual care to hydroxychloroquine) were assessed with the use of contact reports collected in telephone interviews on days 3, 7, and 28.

All testing of nasopharyngeal swabs for SARS-CoV-2 and analyses to determine viral load were performed by technicians who were unaware of previous PCR results, trial-group assignments, and response. PCR amplification was based on the 2019 Novel Coronavirus Real-Time RT [reverse transcriptase]–PCR Diagnostic Panel guidelines of the Centers for Disease Control and Prevention.[14] For quantification, a standard curve was built with the use of 1:5 serial dilutions of a SARS-CoV-2 plasmid (with known concentration) and run in parallel with 300 study samples. The accuracy of the qualitative estimate (i.e., cycle threshold [Ct] values) was determined by correlation with the quantitative measure on 300 samples (Fig. S2). The coefficient of correlation between the two methods was 0.93, which permitted the use of qualitative Ct data to estimate viral load in contacts. Detection of IgM and IgG antibodies was performed by means of fingertip blood testing on the day 14 visit with the use of a rapid test (VivaDiag COVID-19).[15]

OUTCOMES

The primary outcome was the onset of a PCR-confirmed, symptomatic Covid-19 episode, defined as symptomatic illness (at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory or taste disorder, or diarrhea) and a positive RT-PCR test for SARS-CoV-2. The primary outcome was assessed in all asymptomatic contacts, irrespective of the baseline PCR result; in a post hoc analysis, we explored the outcome separately in contacts with a positive baseline PCR test and those with a negative baseline PCR test. The time until the primary event was defined as the number of days until the onset of symptomatic illness from the date of exposure and from the date of randomization.

The secondary outcome was the incidence of SARS-CoV-2 infection, defined as either the RT-PCR detection of SARS-CoV-2 in a nasopharyngeal specimen or the presence of any of the aforementioned symptoms compatible with Covid-19. The rationale for this outcome was to encompass definitions of Covid-19 used elsewhere.[12,16] Contacts who were hospitalized or who died and whose hospital and vital records listed Covid-19 as the main diagnosis (including PCR confirmation) were also considered for the primary and secondary outcomes.

STATISTICAL ANALYSIS

With an enrollment target of 95 clusters per trial group[17] — 15 contacts per cluster and intraclass correlation of 1.0 — the initial design provided a power of 90% to detect a between-group difference of 10 percentage points in the incidence of PCR-confirmed, symptomatic Covid-19, with an expected incidence of 5% in the hydroxychloroquine group and 15% in the usual-care group. Owing to the limited information available by March 2020 regarding the cluster size and the incidence of Covid-19 after exposure, the protocol prespecified a sample-size reestimation at the interim analysis. Reestimation was aimed at maintaining the ability (at 80% power) to detect a between-group difference of 3.5 percentage points in the incidence of primary-outcome events (3.0% in the hydroxychloroquine group and 6.5% in the usual-care group), yielding 320 clusters per trial group with 3.5 contacts per cluster, an intraclass correlation of 1.0, and no provision for crossover.

The primary efficacy analysis was performed in the intention-to-treat population. Multiple imputation by chained equations was applied to account for missing data.[18,19] The assumption that unobserved values were missing at random was deemed to be appropriate because we could not find any pattern among the missing values.[20] A complete-case analysis and a per-protocol analysis were conducted as sensitivity analyses. The cumulative incidence of trial outcomes was compared at the individual level with the use of a binomial regression model with robust sandwich standard errors to account for grouping within clusters.[21] We defined a generalized linear model with a binomial distribution and a log-link function to estimate the risk ratio as a measure of effect.[22] The analyses were adjusted for the baseline variables of age, sex, geographic region, and time of exposure. We performed additional prespecified analyses to assess the consistency of treatment effects in subgroups defined according to the viral load of the contact at baseline, viral load of the index case patient, place of exposure, and time of exposure to the index case patient. The reported confidence intervals have not been adjusted for multiple comparisons and cannot be used to infer effects. Survival curves according to trial group for time-to-event outcomes were compared with the use of a Cox proportional-hazards model with a cluster-level frailty term to adjust for clustering.[23] The significance threshold was set at a two-sided alpha value of 0.05, unless otherwise indicated. All statistical analyses were conducted with R software, version 3.6.2.[24]

RESULTS

CHARACTERISTICS OF THE TRIAL PARTICIPANTS

Between March 17 and April 28, 2020, we assessed 754 index case patients with Covid-19 for eligibility; 672 of them were selected for defining the corresponding clusters, which included 4399 contacts (Fig. 1). A total of 1874 contacts (42.6%) were not enrolled because they met exclusion criteria, including having Covid-19–like symptoms before enrollment (537 contacts). In addition, 40 of 2525 enrolled contacts (1.6%) were excluded from the intention-to-treat analysis because of screening failure, which resulted in an intention-to-treat population of 2485, of whom 171 (6.9%) had missing data imputed on outcome analysis. During follow-up, 64 contacts had a protocol deviation regarding the intervention (per-protocol population of 2250 contacts).

The demographic, clinical, and epidemiologic characteristics of the contacts at baseline were similar in the two trial groups (Table 1). The mean (±SD) age of the contacts was 48.6±19.0 years, and the PCR test at baseline was negative in 87.8% (2000 of 2279). Overall, 39.4% of the contacts (912 of 2314) reported at least one chronic health condition. The median interval from exposure to enrollment was 4.0 days (interquartile range, 3.0 to 6.0). The size of the clusters was similar in the two groups (median, 2.0 contacts in the hydroxychloroquine group and 2.0 in the usual-care group). Exposure was predominantly from an index case patient with a moderate-to-high viral load (10^7 to 10^{12} copies per milliliter), which was reported in 307 of 549 index case patients (55.9%) for whom viral-load data were available. Health care workers and nursing home workers accounted for 1395 of 2314 contacts (60.3%); 626 (27.1%) were household contacts, and 293 (12.7%) were nursing home residents. Overall, 1555 contacts (67.2%) reported routine use of masks at the time of exposure, and 144 contacts (6.2%) continued to sleep in the same room as the index case patient.

PRIMARY OUTCOME

During the 14-day follow-up, 138 of 2314 contacts (6.0%) had a PCR-confirmed, symptomatic Covid-19 episode. The results were similar in the hydroxychloroquine group (64 of 1116; 5.7%) and the usual-care group (74 of 1198; 6.2%) (risk ratio, 0.86; 95% confidence interval [CI], 0.52 to 1.42) (Table 2), with the use of multiple-imputation techniques to account for 171 missing values. The complete-case analysis (Table S1) and per-protocol analysis (Table S2) showed results that were similar to those in the primary analysis. The incidence of each of the components of the primary outcome did not differ substantially between the groups (Table 2).

Overall, the incidence of symptomatic Covid-19 was higher among contacts who had a positive PCR test at baseline than among those who had a negative test (20.4% [64 of 314 contacts] vs.

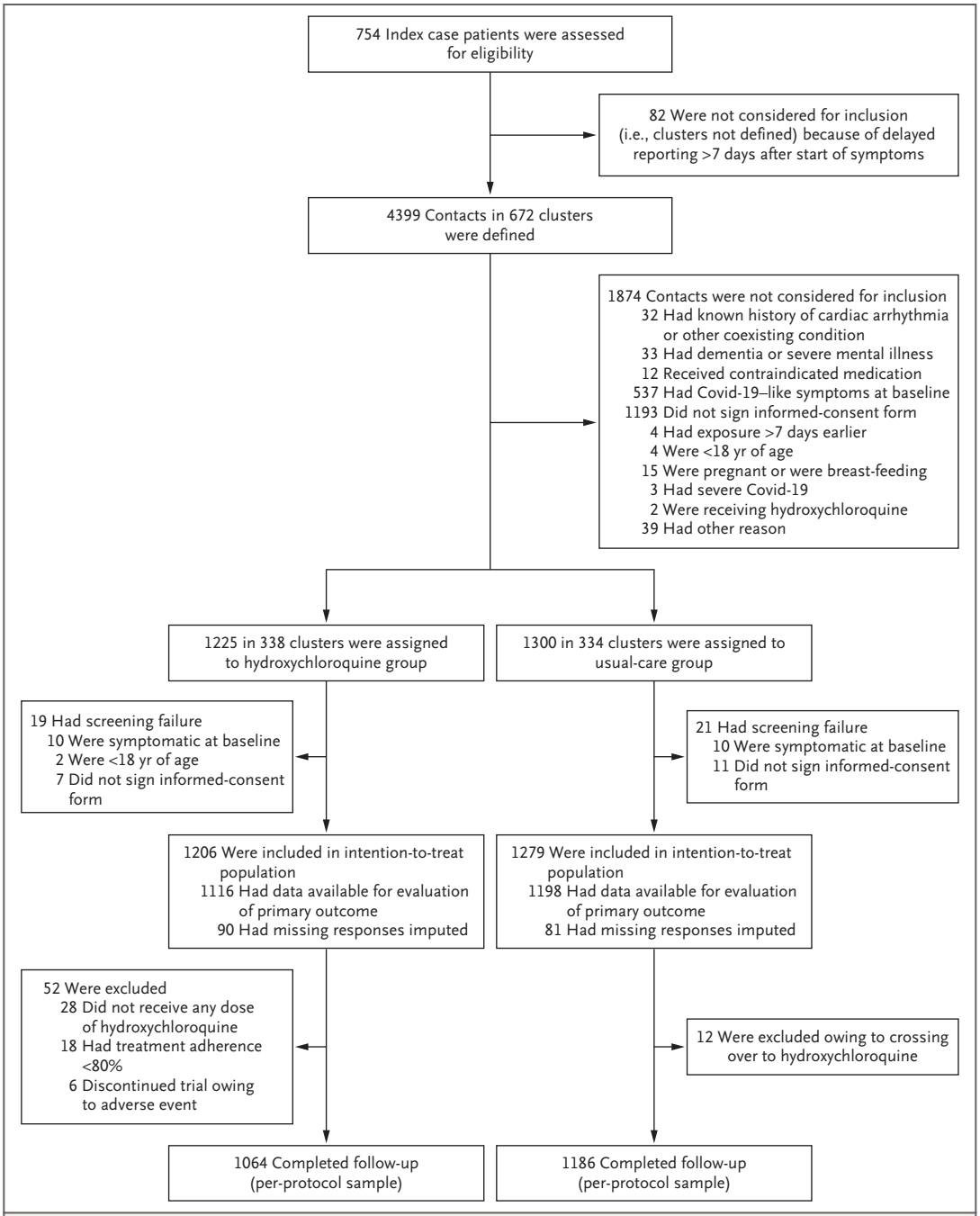

Figure 1. Screening and Randomization.

The safety population (2497 contacts; 1197 in the hydroxychloroquine group and 1300 in the usual-care group) included all those in the intention-to-treat population (except 28 in the hydroxychloroquine group who did not receive the trial medication) plus 40 (19 in the hydroxychloroquine group and 21 in the usual-care group) who were classified as having a screening failure. The intention-to-treat population (2485 contacts; 1206 in the hydroxychloroquine group and 1279 in the usual-care group) included 2314 who had data available for analysis of the primary outcome plus 171 (90 in the hydroxychloroquine group and 81 in the usual-care group) with no available polymerase-chain-reaction (PCR) assay results at day 14 who had missing responses imputed.

Table 1. Characteristics of the Contacts and Their Clusters at Baseline.*

Characteristic	Hydroxychloroquine Group (N=1116)	Usual-Care Group (N=1198)
Contacts of index patients		
Age — yr	48.6±18.7	48.7±19.3
Female sex — no. (%)	813 (72.8)	875 (73.0)
Viral load on PCR at baseline — no./total no. (%)		
Undetectable: $<10^4$ copies/ml	958/1102 (86.9)	1042/1177 (88.5)
10^4 to 10^6 copies/ml	78/1102 (7.1)	88/1177 (7.5)
10^7 to 10^9 copies/ml	58/1102 (5.3)	42/1177 (3.6)
10^{10} to 10^{12} copies/ml	8/1102 (0.7)	5/1177 (0.4)
Coexisting disease — no. (%)		
None	660 (59.1)	742 (61.9)
Cardiovascular disease	82 (7.3)	104 (8.7)
Respiratory disease	47 (4.2)	35 (2.9)
Metabolic disease	68 (6.1)	66 (5.5)
Nervous system disease	97 (8.7)	97 (8.1)
No. of days of exposure before intervention — no. of contacts (%)		
≤3	440 (39.4)	411 (34.3)
4–6	551 (49.4)	668 (55.8)
≥7	125 (11.2)	119 (9.9)
Type of contact with index case patient — no. (%)		
Household contact	302 (27.1)	324 (27.0)
Health care worker	131 (11.7)	130 (10.9)
Nursing home worker	550 (49.3)	584 (48.7)
Nursing home resident	133 (11.9)	160 (13.4)
Routine use of mask — no. (%)†		
Yes	730 (65.4)	825 (68.9)
No	251 (22.5)	256 (21.4)
Missing data	135 (12.1)	117 (9.8)
Sleeping in the same room as the index case patient — no. (%)		
Yes	78 (7.0)	66 (5.5)
No	834 (74.7)	951 (79.4)
Missing data	204 (18.3)	181 (15.1)
Clusters		
Median no. of days of exposure before enrollment (IQR)	4.0 (3.0–6.0)	4.0 (3.0–6.0)
Median no. of contacts per cluster (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Viral load of the index case patient — no./total no. (%)		
Undetectable: $<10^4$ copies/ml‡	42/259 (16.2)	47/290 (16.2)
10^4 to 10^6 copies/ml	68/259 (26.3)	85/290 (29.3)
10^7 or 10^8 copies/ml	81/259 (31.3)	83/290 (28.6)
10^9 to 10^{12} copies/ml	68/259 (26.3)	75/290 (25.9)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and PCR polymerase chain reaction.
† Routine use of mask refers to use at the time of exposure.
‡ The prescreening PCR test was positive at the designated hospital laboratory before enrollment, but the test was negative (undetectable, $<10^4$ copies per milliliter) at the research laboratory from the swab collected on day 1.

Table 2. Primary and Secondary Outcomes.*

Outcome	Hydroxychloroquine Group	Usual-Care Group	Risk Ratio (95% CI)†
	no. of events/no. of contacts (%)		
Primary outcome: PCR-confirmed, symptomatic Covid-19			
All patients‡	64/1116 (5.7)	74/1198 (6.2)	0.86 (0.52–1.42)
Clinical and laboratory criteria	49/1116 (4.4)	60/1198 (5.0)	
Hospital or vital-records criteria	15/1116 (1.3)	14/1198 (1.2)	
PCR-negative at baseline	29/958 (3.0)	45/1042 (4.3)	0.68 (0.34–1.34)
Clinical and laboratory criteria	24/958 (2.5)	37/1042 (3.6)	
Hospital or vital-records criteria	5/958 (0.5)	8/1042 (0.8)	
PCR-positive at baseline	35/158 (22.2)	29/156 (18.6)	1.02 (0.64–1.63)
Clinical and laboratory criteria	25/158 (15.8)	23/156 (14.7)	
Hospital or vital-records criteria	10/158 (6.3)	6/156 (3.8)	
Secondary outcomes§			
Covid-19, either symptomatically compatible or PCR positivity regardless of symptoms	179/958 (18.7)	185/1042 (17.8)	1.03 (0.77–1.38)
Laboratory criteria¶	58/958 (6.1)	67/1042 (6.4)	
Clinical criteria‖	144/958 (15.0)	150/1042 (14.4)	
Hospital or vital-records criteria	5/958 (0.5)	8/1042 (0.8)	
Serologic positivity on day 14	137/958 (14.3)	91/1042 (8.7)	1.57 (0.94–2.62)
IgM positivity	100/958 (10.4)	70/1042 (6.7)	
IgG positivity	118/958 (12.3)	82/1042 (7.9)	

* Percentages are for contacts for whom complete data were available. Covid-19 denotes coronavirus disease 2019.
† Risk ratios were adjusted for contact-level variables (age, sex, geographic region, and time of exposure), and multiple imputation by chained equations[17] was applied to handle missing data. The assumption that unobserved values were missing at random was deemed to be appropriate because we could not find any pattern among the missing values. Because primary and secondary outcomes were dichotomous variables, the imputation models were based on a two-level logistic-regression model to account for clustering.[18] Five estimates from each imputed data set were combined according to Rubin rules.[16]
‡ Marginal estimates of effects for the primary outcome were 5.6% in the hydroxychloroquine group and 6.3% in the usual-care group (risk difference, –0.6 percentage points)
§ Contacts who were PCR-positive at baseline were excluded from the secondary outcomes. The components of the secondary outcomes are not mutually exclusive.
¶ These contacts with PCR-confirmed Covid-19 were either symptomatic or asymptomatic.
‖ These contacts had symptoms compatible with Covid-19, regardless of the results of PCR testing.

3.7% [74 of 2000]) (Table 2). Hydroxychloroquine was ineffective in preventing symptomatic Covid-19 both in contacts with a positive PCR test at baseline and in those with a negative test.

We observed an overall increased risk of symptomatic Covid-19 with increasing viral load of the contact at baseline (Fig. S3A) and increasing viral load of the index case patient (Fig. S3B). The viral load of contacts who went on to have symptomatic Covid-19 increased 4 $\log_{10}$ copies per milliliter throughout the follow-up, whereas that of contacts without Covid-19 remained unchanged (Fig. S3C). Prespecified subgroup analysis of the primary outcome did not reveal substantial between-group differences in the risk of symptomatic Covid-19 according to the viral load of the contact at baseline, the viral load of the index case patient, the duration of exposure, or the type of contact (Fig. 2). The survival analysis of the time to a primary-outcome event showed similar patterns in the two groups regarding symptomatic Covid-19 onset from enrollment (median, 4.0 days in the hydroxychloroquine group and 5.0 days in the usual-care group;

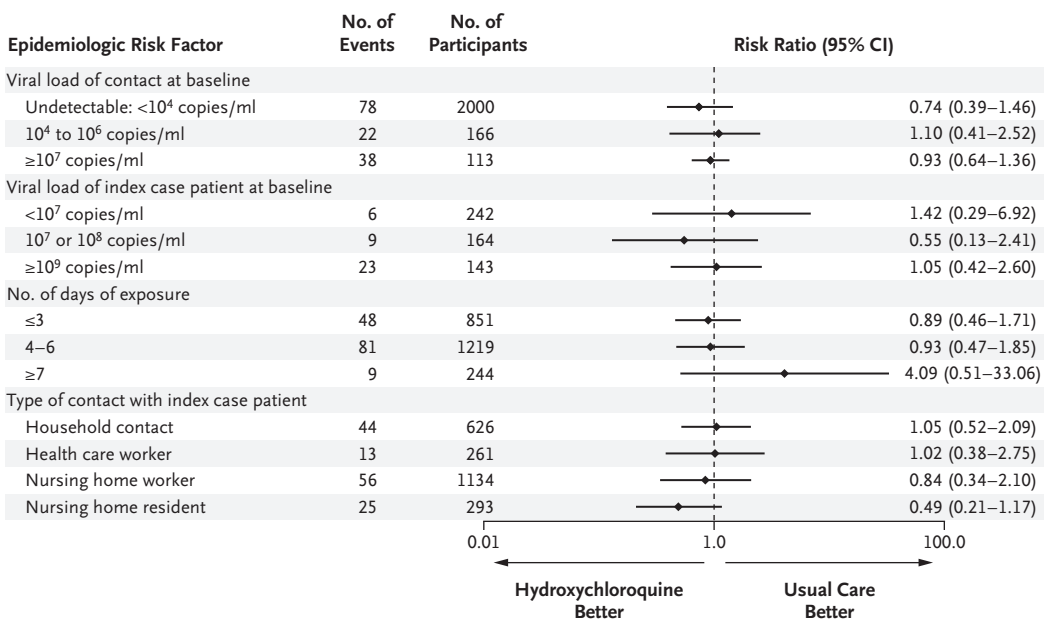

Figure 2. Subgroup Analyses of the Primary Outcome, According to Epidemiologic Risk Factors (Intention-to-Treat Population).

The primary outcome was PCR-confirmed, symptomatic coronavirus disease 2019 within 14 days.

hazard ratio, 0.9 [95% CI, 0.6 to 1.5]) and from exposure (median, 8.0 days and 8.0 days in the respective groups; hazard ratio, 1.0 [95% CI, 0.6 to 1.6]) (Fig. S4).

SECONDARY OUTCOMES

Of the 2000 contacts who tested negative for SARS-CoV-2 on the baseline PCR test, 364 (18.2%) either became PCR-positive or had symptoms compatible with Covid-19 during the follow-up period (Table 2), without a substantial difference between the trial groups (18.7% [179 of 958] with hydroxychloroquine and 17.8% [185 of 1042] with usual care; risk ratio, 1.03 [95% CI, 0.77 to 1.38]). Positivity for virus-specific IgG or IgM antibodies was higher in the hydroxychloroquine group than in the usual-care group (14.3% [137 of 958] vs. 8.7% [91 of 1042]). Of 125 contacts who became PCR-positive during follow-up, 30 (24.0%) were seropositive on day 14 (Fig. S5).

ADHERENCE AND SAFETY

Full adherence to the trial intervention was 95.1% (1138 of 1197) in the hydroxychloroquine group and 97.5% (1268 of 1300) in the usual-care group. In the safety population, 671 of 1197 contacts (56.1%) in the hydroxychloroquine group and 77 of 1300 (5.9%) in the usual-care group had at least one adverse event during 14 days of follow-up (Table 3). The most frequent treatment-related adverse events among contacts given hydroxychloroquine were gastrointestinal (diarrhea, nausea, and abdominal pain) and nervous system disorders (drowsiness and headache) (Table S6). A total of 31 serious adverse events were reported, 14 in the hydroxychloroquine group and 17 in the usual-care group; none of these events were thought to be related to hydroxychloroquine or usual care by the independent pharmacovigilance consultants (Table S7). Six adverse events of special interest were observed, including five episodes of self-limited heart palpitations potentially related to hydroxychloroquine (Table S8). Further safety data are provided in the Supplementary Appendix.

DISCUSSION

In our trial, postexposure prophylaxis with hydroxychloroquine did not prevent SARS-CoV-2 infection or symptomatic Covid-19 in asymptomatic contacts exposed to a PCR-positive index case

Table 3. Adverse Events (Safety Population).*

Event	Hydroxychloroquine Group (N=1197)	Usual-Care Group (N=1300)	P Value
Reported full adherence to trial intervention — no. (%)	1138 (95.1)	1268 (97.5)	
Adverse events — no. (%)			
Any adverse event	671 (56.1)	77 (5.9)	<0.001
Cardiac disorder: palpitations	5 (0.4)	1 (0.1)	
Gastrointestinal disorder: diarrhea, abdominal pain, vomiting	510 (42.6)	33 (2.5)	
Nervous system disorder: headache, taste change, dizziness	260 (21.7)	32 (2.5)	
General disorder: myalgia, fatigue, malaise	103 (8.6)	10 (0.8)	
Intensity of adverse event — no. (%)			<0.001†
Grade 1: mild	573 (47.9)	44 (3.4)	
Grade 2: moderate	68 (5.7)	14 (1.1)	
Grade 3: severe	13 (1.1)	2 (0.2)	
Grade 4: potentially life-threatening	11 (0.9)	10 (0.8)	
Grade 5: death	5 (0.4)	8 (0.6)	
Serious adverse event — no. of events‡	14	17	
Hospitalization	11	12	
Death	5	8	
Treatment-related	0	0	
Adverse event of special interest: cardiac — no. of events§	5	1	

* The safety population included all the contacts who received either hydroxychloroquine or usual care.
† The overall P value for grading is shown.
‡ None of the serious adverse events were adjudicated as being related to hydroxychloroquine or usual care by the independent pharmacovigilance consultants. Death and hospitalization were not mutually exclusive; five deaths occurred at the hospital, whereas other contacts died at a nursing home.
§ Cardiac disorders were all episodes of palpitations; three of five events in the hydroxychloroquine group were adjudicated as being possibly related to the trial drug by the independent pharmacovigilance consultants. Details are provided in the Supplementary Appendix.

patient. The overall attack rate for PCR-confirmed, symptomatic Covid-19 was 6.0%, excluding contacts who were not enrolled because they had symptoms before the baseline assessment. Contacts who received hydroxychloroquine and those who received usual care had a similar incidence of symptomatic Covid-19 (5.7% and 6.2%, respectively). Our trial tested two possible effects of postexposure therapy: prophylaxis in contacts with a negative PCR test at baseline and preemptive therapy in contacts with a positive PCR test at baseline (i.e., to prevent progression of asymptomatic infection to disease). This dual scenario mirrors a real-life setting, in which the PCR result of contacts exposed to a known Covid-19 index case is usually not immediately available. Hydroxychloroquine showed no efficacy as prophylactic therapy for contacts who were PCR-negative at baseline. Similarly, among the contacts who were PCR-positive at baseline (13.6%), hydroxychloroquine had no apparent efficacy as early preemptive therapy. A baseline positive PCR test increased the risk of symptomatic Covid-19 in our cohort, but a high percentage of the contacts with this laboratory result (79.6%) did not go on to have symptomatic disease, thus reinforcing the need to quarantine or to increase testing of contacts even if they are asymptomatic. In addition, of importance to public health decision making is that the higher the SARS-CoV-2 viral load in an index case patient was, the greater was the risk of transmission to contacts.

Hydroxychloroquine also did not reduce the transmission of SARS-CoV-2 (18.7%, as compared with 17.8% with usual care) or the incidence of seropositivity. It is notable that the overlap of a

positive PCR test and a positive serologic test was low, which could be related to the reported low sensitivity of the rapid test for IgM and IgG antibodies within 10 days after symptom onset,[15] the low incidence of seroconversion among asymptomatic contacts,[25] or the higher risk of a false negative PCR result during the initial stage of infection.[16] With respect to safety, we observed a higher incidence of adverse events in the hydroxychloroquine group than in the usual-care group, albeit with low severity. In this open-label trial, the psychological components in the treated group cannot be ruled out. Furthermore, the side effects were mainly gastrointestinal, whereas only 5 of 1479 events (0.3%) in the hydroxychloroquine group were considered to be heart-related; therefore, our data do not corroborate previously published data on the increased risk of cardiac arrhythmia.[26] The safety results need to be interpreted on the basis of the dose used, length of treatment, and lack of electrocardiographic monitoring in the trial.

The strengths of this trial are the use of a PCR test and viral-load quantification at baseline, at day 14, and potentially when the contact was ill, and the measurement of viral load of the index case patient to estimate the risk of transmission. In addition, we included very elderly persons (e.g., >90 years of age) in nursing homes. The trial has some limitations. Unlike the common procedure in clinical trials, the signing of the informed-consent form took place after cluster randomization. Nevertheless, trial-group assignments were revealed to contacts after consent was obtained; therefore, we believe that the strategy for concealing trial-group assignments was appropriate to prevent contacts from choosing to participate or not to participate. Because of the urgency of the pandemic, we did not include a placebo group in the trial, which may have affected the reporting of adverse events. However, the laboratory staff who performed PCR tests remained unaware of the trial-group assignments.

Despite the promising in vitro results that placed hydroxychloroquine among the leading candidates for Covid-19 treatment and prophylaxis,[27-29] there are no compelling data to suggest that hydroxychloroquine is effective. We provide evidence on the lack of efficacy of postexposure prophylaxis therapy with hydroxychloroquine to prevent SARS-CoV-2 infection or symptomatic Covid-19.

Supported by the crowdfunding campaign YoMeCorono (www.yomecorono.com/), Generalitat de Catalunya, Zurich Seguros, Synlab Diagnósticos, Laboratorios Rubió, and Laboratorios Gebro Pharma. Laboratorios Rubió donated and supplied the hydroxychloroquine (Dolquine).

Dr. Tebé reports receiving consulting fees from Boehringer Ingelheim and lecture fees from Amgen. No other potential conflict of interest relevant to this article was reported.

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.

We thank Gerard Carot-Sans for providing medical writing support with an earlier version of the manuscript, Eric Ubals (Pierce AB) and Òscar Palao (Opentic) for website and database management, Óscar Camps and the staff of Open Arms (a nongovernmental organization) for nursing home operations, Anna Valentí and the staff of the human resources department at Hospital Germans Trias i Pujol for telephone monitoring, Marc Clotet and Natalia Sánchez for coordinating the YoMeCorono crowdfunding campaign, and the members of the institutional review board at Hospital Germans Trias i Pujol and the Spanish Agency of Medicines and Medical Devices for their prompt action for consideration and approvals of the protocol.

APPENDIX

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versitat de Barcelona (S.S.), and Agència de Qualitat i Avaluació Sanitàries de Catalunya (C.V., R.M.V.-H.), Barcelona, Bellvitge Biomedical Research Institute, L'Hospitalet de Llobregat (C.T., J. Peñafiel), Gerència Territorial de Catalunya Central, Institut Català de la Salut, Sant Fruitós de Bages (A.F.), Xarxa Santa Tecla Sanitària i Social, Tarragona (G.F.-M.), Entitat de Base Asociativa Centelles–Atenció Primària, Centelles (S.N.), Gerència Territorial de Àmbit Metropolità Nord, Institut Català de la Salut, Sabadell (N.P.), Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública, Madrid (J.C.), and Universitat de Vic–Universitat Central de Catalunya, Vic (O.M., B.C.) — all in Spain; and Lihir Medical Center–International SOS, Lihir Island, Papua New Guinea (O.M.).

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