

# 1 A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and 2 Disease

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## 48 **ABSTRACT**

### 49 *Background*

50 Current strategies for preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)  
51 infections are limited to non-pharmacological interventions. Hydroxychloroquine (HCQ) has been  
52 proposed as a postexposure therapy to prevent Coronavirus disease 2019 (Covid-19) but definitive  
53 evidence is lacking.

### 54 *Methods*

55 We conducted an open-label, cluster-randomized trial including asymptomatic contacts exposed to a  
56 PCR-positive Covid-19 case in Catalonia, Spain. Clusters were randomized to receive no specific therapy  
57 (control arm) or HCQ 800mg once, followed by 400mg daily for 6 days (intervention arm). The primary  
58 outcome was PCR-confirmed symptomatic Covid-19 within 14 days. The secondary outcome was SARS-  
59 CoV-2 infection, either symptomatically compatible or a PCR-positive result regardless of symptoms.  
60 Adverse events (AEs) were assessed up to 28 days.

### 61 *Results*

62 The analysis included 2,314 healthy contacts of 672 Covid-19 index cases identified between Mar 17 and  
63 Apr 28, 2020. A total of 1,198 were randomly allocated to usual care and 1,116 to HCQ therapy. There  
64 was no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease  
65 (6.2% usual care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54-1.46]), nor evidence of  
66 beneficial effects on prevention of SARS-CoV-2 transmission (17.8% usual care vs. 18.7% HCQ). The  
67 incidence of AEs was higher in the intervention arm than in the control arm (5.9% usual care vs 51.6%  
68 HCQ), but no treatment-related serious AEs were reported.

### 69 *Conclusions*

70 Postexposure therapy with HCQ did not prevent SARS-CoV-2 disease and infection in healthy  
71 individuals exposed to a PCR-positive case. Our findings do not support HCQ as postexposure  
72 prophylaxis for Covid-19.

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75

## 76 INTRODUCTION

77 Coronavirus 2019 disease (Covid-19) is a rapidly emerging infection caused by the severe acute  
78 respiratory syndrome coronavirus 2 (SARS-CoV-2). The rate of new cases among contacts (secondary  
79 attack rate) has been estimated as 10 to 15%.<sup>1-4</sup> The current infection control strategy is based on social  
80 distancing and isolation of cases and contacts.<sup>5</sup> The effectiveness of the latter depends on the promptness  
81 of the intervention, level of contact tracing, and level of isolation compliance.<sup>6</sup> Unfortunately, real-world  
82 constraints for implementing full effective measures have resulted in SARS-CoV-2 spread in many  
83 countries.

84 Postexposure prophylaxis of healthy contacts is among the measures used for outbreak control of several  
85 infectious diseases, for example, in pandemic influenza.<sup>7</sup> No agent is known to be effective in preventing  
86 SARS-CoV-2 infection or disease, but several drugs have shown antiviral activity in the laboratory,  
87 including the aminoquinolines hydroxychloroquine (HCQ) and chloroquine.<sup>8</sup> In-vitro results showed that  
88 these drugs block the SARS-CoV-2 viral spread in cell cultures<sup>9-11</sup> and that HCQ was more effective at  
89 impairing SARS-CoV-2 viral replication compared to chloroquine.<sup>11</sup> To date, only one RCT has reported  
90 on HCQ for postexposure prophylaxis for Covid-19.<sup>12</sup> However, concerns have been raised about the trial  
91 design, primarily because most participants were diagnosed with an influenza-like illness based on  
92 symptoms alone, and only 20% of their Covid-19 outcome was confirmed with PCR.

93 We investigated the efficacy and safety of HCQ to prevent secondary PCR-confirmed symptomatic  
94 Covid-19 (confirmed Covid-19) and SARS-CoV-2 infection in contacts exposed to a PCR-positive  
95 Covid-19 case during the outbreak in Catalonia, the region with the second highest number of Covid-19  
96 cases in Spain.

97

## 98 **METHODS**

### 99 *PARTICIPANTS*

100 We included adult individuals  $\geq 18$  years of age with a recent history of close contact exposure to a PCR-  
101 confirmed Covid-19 case (i.e.,  $> 15$  minutes within two meters, up to seven days before enrolment) and  
102 absence of Covid-19-like symptoms on the two weeks preceding enrolment, as either a healthcare worker,  
103 a household contact, a nursing home worker or a nursing home resident. Contacts with Covid-19-like  
104 signs and symptoms at the time of the baseline visit were considered unpreventable Covid-19 events and  
105 were not enrolled in the study. All eligibility criteria are listed in the Supplementary Appendix.

### 106 *TRIAL DESIGN AND OVERSIGHT*

107 This was an open-label, phase 3 cluster-randomized trial conducted from Mar 17 to Apr 28, 2020, during  
108 the Covid-19 outbreak, in three out of nine health administrative regions in Catalonia, Spain: *Catalunya*  
109 *central*, *Àmbit Metropolità Nord*, and *Barcelona Ciutat* (total target population 4,206,440 people; Fig. S1,  
110 Supplementary Appendix).

111 Study candidates were screened using the electronic registry of the Epidemiological Surveillance  
112 Emergency Service of Catalonia (SUVEC) of the Department of Health. During the Covid-19 outbreak in  
113 Catalonia, a public health ordinance required all patients who tested positive for Covid-19 in any of the  
114 designated diagnostic laboratories to be notified to the SUVEC.<sup>13</sup>

115 The study protocol and subsequent amendments, available at NEJM.org, were approved by the  
116 institutional review board of Hospital Germans Trias Pujol, and the Spanish Agency of Medicines and  
117 Medical Devices. All participants provided written informed consent.

### 118 *TRIAL PROCEDURES*

119 Following a similar approach as the ring vaccination trial “Ebola Ça Suffit!”,<sup>14</sup> we defined study clusters  
120 (called rings) of healthy individuals (contacts) epidemiologically linked to a PCR-positive Covid-19 case

121 (index case). All contacts in a ring were simultaneously cluster-randomized (1:1) to either a control arm  
122 or an intervention arm. Randomization was performed remotely by a member of the study team not  
123 involved in participants' enrollment. Following ring randomization, we verified the selection criteria of  
124 individual candidates and obtained informed consent for enrollment. The allocation was revealed to  
125 participants after providing written consent on day 1 (baseline). Participants allocated in the control arm  
126 received no treatment aside from usual care, whereas those in the intervention arm received HCQ  
127 (Dolquine<sup>®</sup>) 800 mg on day 1, followed by 400 mg once daily for six days. The dose and regimen of HCQ  
128 were chosen based on pharmacokinetic simulations to achieve plasma and lung concentrations above the  
129 SARS-CoV-2 half-maximal effective concentration observed in-vitro<sup>11</sup> for 14 days (details provided in  
130 the Study Protocol).

131 By the time of trial conduct, quarantine was mandatory for all exposed contacts, according to the National  
132 Department of Health guidelines; hence the likelihood that a participant could be exposed to other cases  
133 was low. Covid-19 index cases that generated the rings were enrolled in a nested trial aimed at  
134 investigating the efficacy of early treatment with hydroxychloroquine as therapeutic intervention for  
135 Covid-19 outpatients. Laboratory technicians were unaware of participants' treatment, treatment  
136 response, and previous PCR results during the entire follow-up period.

137 All contacts were visited at home or workplace on day 1 for medical exam, and baseline nasopharyngeal  
138 swab collection for SARS-CoV-2 RT-PCR test and viral load. Symptoms surveillance consisted of active  
139 monitoring by phone on days 3 and 7, and passive monitoring whenever the participant developed  
140 symptoms (i.e., participants were advised to call the research team). Participants who developed  
141 symptoms were visited the same day (unscheduled visit) by the outbreak field team for nasopharyngeal  
142 swab collection. All participants were visited at home on day 14 for nasopharyngeal swab collection, and  
143 finger-prick for IgM/IgG rapid test. Safety, medication adherence (i.e., treatment and number of doses  
144 taken), and crossover (i.e., unplanned conversion of control to intervention) were assessed using self-  
145 reports collected in telephone interviews on days 3, 7, and 28. Details on procedures performed at each

146 visit and laboratory methods for SARS-CoV-2 identification and quantification (Fig. S2) are provided in  
147 the Supplementary Appendix.

#### 148 *OUTCOMES*

149 The primary outcome was the onset of a confirmed Covid-19 episode, defined as symptomatic illness (at  
150 least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat,  
151 new olfactory and taste disorder(s), or diarrhea) and a positive SARS-CoV-2 RT-PCR test. The primary  
152 outcome was assessed in all asymptomatic individuals, irrespective of the PCR result; in a post hoc  
153 analysis, we explored the outcome in individuals with positive and negative PCR separately. Time-to-  
154 event was defined as the number of days from the date of randomization/exposure to the confirmed date  
155 of the onset of symptomatic illness.

156 The secondary outcome was the incidence of SARS-CoV-2 infection, defined as either the RT-PCR  
157 detection of SARS-CoV-2 in a nasopharyngeal specimen or the presence of any of the aforementioned  
158 symptoms compatible with Covid-19. The rationale for this outcome was to encompass definitions of  
159 Covid-19 used elsewhere<sup>12,15</sup> and all possible viral dynamics. We, therefore, assumed that if clinical  
160 suspicion is high, infection should not be ruled out based on a negative PCR alone—particularly early in  
161 the course of infection.<sup>15</sup> Participants who were hospitalized or died and whose hospital/vital records  
162 listed Covid-19 as the main diagnosis (including PCR confirmation) were also considered for the primary  
163 and secondary outcomes. We also measured serological positivity (IgM/IgG) of contacts at day 14. Safety  
164 outcomes included the frequency and severity of adverse events (AE), serious AE (SAE), and AE of  
165 special interest (e.g., cardiac) up to 28 days from treatment start. Causality was assessed by an external  
166 panel of pharmacovigilance consultants.

#### 167 *STATISTICAL ANALYSIS*

168 With an enrollment target of 95 clusters per trial group<sup>16</sup> —15 participants per cluster and intraclass  
169 correlation of 1.0— the initial design yielded 90% power to detect a difference of 10% in the incidence,

170 with expected incidence of 15% in the control arm. Owing to the limited information available by March  
171 2020 regarding the cluster size and the incidence of Covid-19 after exposure, the protocol prespecified a  
172 sample-size re-estimation at the interim analysis. This re-estimation was aimed at maintaining the ability  
173 (80% power) to detect a reduction from 6.5% to 3% of the primary outcome, yielding 320 clusters per  
174 trial group with 3.5 participants per cluster.

175 The primary efficacy analysis was performed on the intention-to-treat (ITT) population, which included  
176 all randomized subjects with complete outcome data. We decided not to impute outcome data to  
177 participants with missing measurements because this approach would have biased the incidence of  
178 secondary Covid-19 events. Sensitivity analyses were performed with the per-protocol (PP) population in  
179 participants who completed the trial according to the protocol. The safety population included all  
180 participants who received any trial intervention, including usual care.

181 The cumulative incidence in primary, secondary, and safety outcomes was compared at the individual  
182 level using a binomial regression model with robust sandwich standard errors to account for clustering  
183 within rings.<sup>17</sup> We defined a generalized linear model with a binomial distribution and a logarithm link  
184 function to estimate the relative risk (RR) as a measure of effect.<sup>18</sup> The individual-level variables we  
185 adjusted for are age, gender, region, and time of exposure. We did additional pre-specified analyses to  
186 assess the consistency of treatment effects in subgroups defined according to the viral load of the contact  
187 at baseline, viral load of the index case, place of exposure, time of exposure to the index case. Survival  
188 curves by study groups on time-to-event outcomes were compared using a Cox proportional hazards  
189 model with a cluster-level frailty term to adjust for clustering.<sup>19</sup> The significance threshold was set at a  
190 two-sided alpha value of 0.05, unless otherwise indicated, and all statistical analyses were conducted in R  
191 version 3.6.2.<sup>20</sup>



## 192 **RESULTS**

### 193 *CHARACTERISTICS OF STUDY PARTICIPANTS*

194 Between Mar 17 and Apr 28, 2020, we assessed 754 Covid-19 index cases for eligibility; 672 of them  
195 were selected for defining the corresponding clusters, which included 4,399 contacts (Fig. 1). 1,874  
196 (42.6%) of the 4,399 contacts were not enrolled because of at least one exclusion criteria, including  
197 contacts presenting Covid-19-like symptoms before enrolment ( $n = 537$ ). Additionally, 211 (8.4%) of  
198 2,525 enrolled contacts were excluded from ITT analysis because of screening failure or missing PCR  
199 results on day 14, yielding an ITT population of 2,314 contacts. During follow-up, 64 participants had a  
200 protocol deviation regarding the intervention (PP population of 2,250 contacts).

201 The demographic, clinical, and epidemiological characteristics of participants at baseline were similar in  
202 the two study arms (Table 1, PP analysis in the Supplementary Appendix). The mean age of contacts was  
203 48.6 years (SD 19.0) and the PCR test at baseline was negative in 87.8% of them (2,000 of 2,314).  
204 Overall, 55.6% of the participants (1,287 of 2,314) reported chronic health conditions. The median length  
205 from exposure to enrolment was 4.0 (IQR 3.0–6.0) days. The size of clusters was similar in both arms  
206 (median 2.0 vs. 2.0;  $P = 0.25$ ). Exposure was predominantly from an index case with moderate-to-high  
207 viral load shedding (460 of 549 [83.8%] index cases with available viral load assessment). Health care  
208 workers and nursing home workers accounted for 60.3% (1,395) of the participants; 27.7% (640) were  
209 enrolled as household contacts, and 12.7% (293) as nursing home residents. Overall, 67.2% (1,555) of  
210 participants reported routine use of masks at the time of exposure, and 6.2% (144) of contacts continued  
211 to sleep in the same room as the index case.

### 212 *PRIMARY OUTCOME*

213 During the 14-day follow-up, 138 (6.0%) of 2,314 participants experienced a PCR-confirmed,  
214 symptomatic Covid-19 episode. The primary outcome was similar in the control arm (6.2%; 74/1,198)

215 and the intervention arm (5.7%; 64/1,116; RR 0.89 [95% CI 0.54–1.46]) (Table 2). The incidence of each  
216 of the components of the primary outcome did not differ significantly between groups.

217 Overall, the incidence of confirmed Covid-19 was higher in participants who tested positive in the  
218 baseline PCR (Table 2); 3.4% (74 of 2,000) participants with a negative PCR at baseline and 21.9% (61  
219 of 279) participants with a positive PCR at baseline met the primary outcome criteria. The intervention  
220 was ineffective, regardless of the PCR result at baseline.

221 We observed an overall increased risk of Covid-19 with increasing viral load of the participant at baseline  
222 (Fig. 2A) and increasing viral load of the index case (Fig. 2B). The viral load of contacts who developed  
223 confirmed Covid-19 increased 4 log<sub>10</sub> copies/mL throughout the follow-up, whereas that of contacts  
224 without Covid-19 remained unchanged (Fig. 2C). Pre-specified subgroup analysis of the primary outcome  
225 did not reveal between-group differences in the risk of Covid-19 according to the viral load of the  
226 participant at baseline, the viral load of the index case, the length of exposure, or the place of contact (Fig.  
227 3).

228 The survival analysis of the time to the primary outcome showed similar patterns in the two arms  
229 regarding confirmed Covid-19 onset from enrolment (median 14.0 vs. 14.0 days in the control and  
230 intervention arms, respectively; HR 0.9 [95%CI 0.6–1.5]) and from exposure (median 18.0 vs. 18.0 days;  
231 HR 1.0 [0.6–1.6]) (Fig. S3).

### 232 *SECONDARY OUTCOMES*

233 Of the 2,000 participants who tested negative for SARS-CoV-2 in the baseline PCR, 364 (18.2%) either  
234 became PCR positive or developed symptoms compatible with Covid-19 throughout the follow-up period  
235 (secondary outcome, Table 2), without differences between study arms (17.8%, 185/1,042 control vs.  
236 18.7%, 179/958 intervention; RR 1.04 [95%CI 0.77 1.41]). The virus-specific IgG/IgM positivity was  
237 higher in the intervention arm than in the control arm (6.7%, 70/1,042 control vs. 10.4% 100/958). Of 125

238 participants who became PCR-positive during follow-up, 30 (24.0%) were seropositive on day 14 (Fig  
239 S4).

#### 240 *ADHERENCE AND SAFETY*

241 Full adherence for the trial intervention was 97.5% (1,268 of 1,300) in the control arm and 95.1% (1,138  
242 of 1,1197) in the intervention arm. In the safety population, 77/1,300 (5.9%) participants in the control  
243 arm and 671/1,197 (51.6%) in the intervention arm experienced at least one AE during 14 days of follow-  
244 up (Table 3). The most frequent treatment-related AEs among participants given HCQ were  
245 gastrointestinal (diarrhea, nausea, and abdominal pain) and nervous system disorders (drowsiness,  
246 headache, and metallic taste) (Tables S4). Thirty-one SAE were reported, 17 in the control arm and 14 in  
247 the intervention arm, none of them related to HCQ (Table S5). Six AEs of special interest were observed,  
248 including five episodes of self-limited palpitations potentially related to treatment (Table S6). Relevant  
249 safety data listings are provided in the Supplementary Appendix.

250

## 251 **DISCUSSION**

252 Postexposure prophylaxis with HCQ did not prevent Covid-19 disease or SARS-CoV-2 infection in  
253 asymptomatic contacts exposed to a PCR-positive index case. In our cohort, the overall attack rate for the  
254 PCR-confirmed symptomatic Covid-19 was 6.0%, excluding subjects that were not enrolled because had  
255 symptoms before the baseline assessment. HCQ did not decrease the incidence of confirmed Covid-19  
256 disease among contacts (6.2 vs. 5.7%). Our trial tested two possible effects of postexposure therapy:  
257 prophylaxis in contacts with negative PCR at baseline, and preemptive therapy in contacts with positive  
258 PCR at baseline (i.e., prevent progression of asymptomatic infection to disease). This dual scenario  
259 mirrors a real-life setting, where the PCR result of people exposed to a known Covid-19 case is usually  
260 not available immediately. Among PCR positive contacts at baseline (12% of subjects), the intervention  
261 had no apparent efficacy as early preemptive therapy. Of note a baseline positive PCR result significantly

262 increased the risk of developing Covid-19 in our cohort, but a high proportion of participants with this lab  
263 result (79%) did not go on to develop symptomatic disease, thus reinforcing the need to quarantine or to  
264 increase testing of contacts even if asymptomatic. Also, of importance to the public health decision-  
265 making is that high Covid-19 viral load ( $>10^8$  log<sub>10</sub> copies/mL (SD)) results in more risk of transmission to  
266 contacts.

267 The intervention also did not reduce the transmission of SARS-CoV-2 (17.8% vs. 18.7%) or incidence of  
268 seropositivity. Notably, the overlap of positive PCR and positive serology was low, which could be  
269 related to both, the reported low rate of seroconversion in asymptomatic contacts<sup>21</sup> or the higher risk of  
270 false negative PCR result on the initial stage of infection.<sup>15</sup> Regarding safety, we observed a higher  
271 incidence of AE in the treatment group, albeit with low severity. This is an open-label study where the  
272 psychological components in the treated group cannot be excluded. Furthermore, the side effects reported  
273 were mainly at gastrointestinal level, while only five (0.3%) out of 1,479 events could be considered  
274 cardiac, thus not confirming previously published data that raised safety concerns.<sup>22</sup> The safety results  
275 need to be interpreted considering the dose used, length of treatment, and the lack of ECG monitoring in  
276 the study.

277 The strengths of this study are the use of PCR and viral load titration at baseline, at day 14, and  
278 potentially when ill, and the measurement of viral load of the source index case to estimate risk of  
279 transmission. In addition, we included elderly persons (e.g. ages >90 years of age) from nursing homes.  
280 The study has some limitations. Unlike the common procedure in clinical trials, the informed consent  
281 signature took place after cluster-randomization. Nevertheless, allocation was revealed to participants  
282 after consent signature, therefore we believe the allocation concealment strategy was appropriate to  
283 prevent study participants from choosing to participate or not to participate. Owing to the urgency, the  
284 trial could not be masked with a placebo, which affected the rate of AE declared (AEs are not commonly  
285 reported in the control, non-placebo group), but it did not affect the attrition numbers in the control arm.

286 However, it is worth mentioning that the laboratory staff who performed PCR tests remained unaware of  
287 the allocation of each sample.

288 Despite the promising in-vitro results that placed HCQ among the leading candidates for Covid-19  
289 treatment and prophylaxis,<sup>23–25</sup> to date there is no strong argument to suggest that HCQ is effective. We  
290 provide high-quality evidence on the lack of efficacy of postexposure prophylaxis therapy with HCQ to  
291 prevent Covid-19 disease or SARS-CoV-2 infection. The data presented in this report is particularly  
292 valuable for the scientific community and policymakers involved in controlling the pandemic at the  
293 population level. Our findings encourage directing efforts to other antiviral candidates for postexposure  
294 prophylaxis.

## 295 **CONTRIBUTORS**

296 OM, LB, BC, CV, RMV, JC, CGB, MVM conceived, designed and wrote the manuscript,  
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298 contributed to the recruitment, clinical care, and follow-up of patients,  
299 CT, AT, CL, EM, JP JR, AS, JZ, EM, JRU, SS analyzed and managed data  
300 JA, JMA, JC, RF, MF analyzed data and reviewed the manuscript  
301 EB, PC, ERM, LR Did all laboratory tests  
302 JM, MC, MS, SG directed and managed the planning and execution of the project  
303 All authors reviewed and approved the final version of the manuscript  
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310

311 **CONFLICTS OF INTEREST**

312 We declare no conflicts of interest

313

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328

329

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394

## 395 **Figure legends**

396

397

398 **Figure 1.** Flow diagram of individual selection and allocation.

399

400 Legend. The safety population (n=2,497; 1,300 in the control arm and 1,197 in the intervention arm)  
401 included all individuals in the ITT population (except 28 not receiving any dose of study medication) plus  
402 211 participants that received medication but were excluded from ITT because of screening-failure, or  
403 missing PCR results on Day 14.

404

405 **Figure 2.** Association of baseline viral load of participants and viral load of their index case with  
406 breakthrough Covid-19 (ITT population)

407 Legend. Panels A and B show the association of the participant's viral load at baseline (A) and viral load  
408 of the index case (B) with the likelihood of developing PCR-confirmed symptomatic Covid-19 in the  
409 overall intention-to-treat population (aggregated data for the control and intervention arms). The dots are  
410 participants with (=1) or without (=0) the primary outcome of PCR-confirmed Covid-19. Panel C shows  
411 the viral load increase from baseline in participants who developed or did not develop Covid-19 (details  
412 are provided in Table S2, Supplementary Appendix).

413

414 **Figure 3.** Subgroup analyses for the primary outcome according to risk of exposure factors (ITT  
415 population)

416

417 **Tables**

418 **Table 1.** Baseline characteristics of study participants (contacts) included in the intention-to-treat  
 419 population (N=2314).  
 420

	<b>Control arm</b> (N=1,198)	<b>Intervention arm</b> (N=1,116)
<b>Individuals' characteristics</b>		
Age (years), <i>mean (SD)</i>	48.7 (19.3)	48.6 (18.7)
Gender (female), <i>n (%)</i>	875 (73.0%)	813 (72.8%)
PCR result at baseline, <i>n (%)</i> (N=2279) *		
Undetectable (< 10 <sup>4</sup> copies/mL)	1042 (88.5%)	958 (86.9%)
10 <sup>4</sup> -10 <sup>6</sup> copies/mL	88 (7.5%)	78 (7.1%)
10 <sup>7</sup> -10 <sup>9</sup> copies/mL	42 (3.6%)	58 (5.3%)
10 <sup>10</sup> -10 <sup>12</sup> copies/mL	5 (0.4%)	8 (0.7%)
<b>Coexisting disease</b>		
None	547 (45.7%)	480 (43.0%)
Cardiovascular disease	178 (14.9%)	130 (11.6%)
Respiratory disease	47 (3.9%)	64 (5.7%)
Metabolic disease	94 (7.8%)	99 (8.9%)
Nervous system disease	170 (14.2%)	170 (15.2%)
<b>Characteristics of clusters</b>		
Number of days of exposure before enrollment, <i>median (IQR)</i>	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)
Number of days of exposure before the intervention, N (%)		
≤3 days	411 (34.3%)	440 (39.4%)
4-6 days	668 (55.8%)	551 (49.3%)
≥7 days	119 (9.9%)	125 (11.2%)
Size of clusters, <i>median (IQR)</i>	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
Viral load of the index case, <i>n (%)</i> (N=549)		
Undetectable (< 10 <sup>4</sup> copies/mL) †	47 (16.2%)	42 (16.2%)
10 <sup>4</sup> -10 <sup>6</sup> copies/mL	85 (29.3%)	68 (26.3%)
10 <sup>7</sup> -10 <sup>9</sup> copies/mL	125 (43.1%)	129 (49.8%)
10 <sup>10</sup> -10 <sup>12</sup> copies/mL	33 (11.4%)	20 (7.7%)
Type of contact with index case, <i>n (%)</i>		
Household contact	338 (28.2%)	302 (27.1%)
Healthcare worker	130 (10.9%)	131 (11.7%)
Nursing home worker	584 (48.7%)	550 (49.3%)
Nursing home resident	160 (13.4%)	133 (11.9%)
Routine use of mask, <i>n (%)</i> ‡		
Yes	825 (68.9%)	730 (65.4%)
No	256 (21.4%)	251 (22.5%)
NA	117 (9.7%)	135 (12.1%)
Sleeping in the same room as the index case, <i>n (%)</i>		
Yes	66 (5.51%)	78 (6.99%)
No	951 (79.4%)	834 (74.7%)
NA	181 (15.1%)	204 (18.3%)

421 **IQR:** interquartile range (i.e., 25<sup>th</sup> and 75<sup>th</sup> percentiles). **NA:** not available. **SD:** standard deviation.  
 422

423 \* Baseline PCR result was not available for 21 participants in the control arm and 14 participants in the intervention  
424 arm.

425 † Pre-screening PCR was positive at the designated hospital lab prior to enrollment, but the result was negative  
426 (undetectable < 10<sup>4</sup> copies/mL) at the research lab from the swab collected on day 1.

427 ‡ Routine use of mask refers to use at the time of exposure.

428

429

430 **Table 2.** Outcomes of hydroxychloroquine prophylaxis against Covid-19 (intention-to-treat population).  
431

	<b>Control arm</b>	<b>Intervention arm</b>	
	<b>Events (%)</b>	<b>Events (%)</b>	<b>RR* (95% CI)</b>
<b>Primary outcome</b>	N=1198	N=1116	
<b>Overall (N = 2,314)</b>			
PCR confirmed symptomatic Covid19	74 (6.2%)	64 (5.7%)	0.89 (0.54, 1.46)
Clinical and laboratory criteria	60 (5.0%)	49 (4.4%)	
Hospital or vital records criteria	14 (1.2%)	15 (1.3%)	
<b>PCR (-) at baseline (N =2000)</b>	N=1042	N=958	
PCR-confirmed symptomatic Covid19	45 (4.3%)	29 (3.0%)	1.45 (0.73, 2.88)
Clinical and laboratory criteria	37 (3.6%)	24 (2.5%)	
Hospital or vital records criteria	8 (0.8%)	5 (0.5%)	
<b>PCR (+) at baseline (N=314)</b>	N=156	N=158	
PCR-confirmed symptomatic Covid19	29 (18.6%)	35 (22.2%)	0.96 (0.58, 1.58)
Clinical and laboratory criteria	23 (14.7%)	25 (15.8%)	
Hospital or vital records criteria	6 (3.9%)	10 (6.3%)	
<b>Secondary outcomes (N= 2,000) †</b>	N=1042	N=958	
Covid19 either symptomatically compatible or PCR positivity regardless of symptoms	185 (17.8%)	179 (18.7%)	1.04 (0.77, 1.41)
Laboratory criteria ‡	67 (6.4%)	58 (6.1%)	
Clinical criteria □	150 (14.4%)	144 (15.0%)	
Hospital or vital records criteria	8 (9.7%)	5 (0.5%)	
Serology positivity on day 14	91 (8.7%)	137 (14.3%)	1.6 (0.96, 2.69)
IgM positivity	70 (6.7%)	100 (10.4%)	
IgG positivity	82 (7.9%)	118 (12.3%)	

432  
433 **RR:** Risk ratio. **CI:** confidence interval.  
434 \* Risk ratios are adjusted for contact-level variables (age, gender, region, and time of exposure).  
435 † Excluding PCR positive at baseline.  
436 ‡ PCR confirmed either symptomatic or asymptomatic.  
437 □ Symptoms compatible with Covid-19 regardless of PCR result  
438 The components of the primary and secondary outcomes are not mutually exclusive.  
439  
440

442 **Table 3.** No. of subjects experiencing at least one AE (Safety population).

	Control arm N=1,300	Intervention arm N=1,197	P-value
Reported full adherence to trial intervention	1,268 (97.5%)	1,138 (95.1%)	
Adverse events			
Any AE	77 (5.9%)	671 (51.6%)	<0.001
Cardiac disorder (palpitations)	1 (0.1%)	5 (0.4%)	
Gastrointestinal disorder (diarrhea, abdominal pain, and vomiting)	33 (2.5%)	510 (42.6%)	
Nervous system disorder (headache, taste change, dizziness)	32 (2.5%)	260 (21.7%)	
General disorder (myalgia, fatigue, malaise)	10 (0.8%)	103 (8.6%)	
Intensity			<0.001*
Grade 1	44 (3.4%)	573 (44.1%)	
Grade 2	14 (1.1%)	68 (5.2%)	
Grade 3	2 (0.2%)	13 (1.0%)	
Grade 4	10 (0.8%)	11 (0.8%)	
Grade 5	7 (0.5%)	6 (0.5%)	
Serious AE †	17	14	
Hospitalization	12	11	
Deaths	8	5	
Treatment-related Serious AE	0	0	
AE of special interest (cardiac) ‡	1	5	

443  
 444 \* overall p-value for grading  
 445 † None of the serious adverse events (SAE) were adjudicated as related to HCQ by the pharmacovigilance  
 446 consultants.  
 447 Death and hospitalization were not mutually exclusive; five deaths occurred at the hospital while other participants  
 448 died at a nursing home.  
 449 ‡ Cardiac disorders were all palpitations episodes; 3 of 5 events in the intervention arm were adjudicated as possibly  
 450 related to the study drug by the independent pharmacovigilance consultants. Details are provided in Table S6  
 451 (Supplementary material).  
 452







