Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Infectious Diseases 106 (2021) 314–322

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial

Raymond Chee Seong Seet[a,b,*], Amy May Lin Quek[a,b], Delicia Shu Qin Ooi[c,d], Sharmila Sengupta[e], Satish Ramapatna Lakshminarasappa[f], Chieh Yang Koo[g], Jimmy Bok Yan So[h], Boon Cher Goh[i], Kwok Seng Loh[j], Dale Fisher[a,e], Hock Luen Teoh[a,b], Jie Sun[k], Alex R. Cook[k], Paul Anantharajah Tambyah[a,e], Mikael Hartman[h,k]

[a] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[b] Division of Neurology, Department of Medicine, National University Hospital, Singapore
[c] Department of Pediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[d] Division of Pediatric Endocrinology, Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, Singapore
[e] Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore
[f] Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[g] Department of Cardiology, National University Heart Centre, Singapore
[h] Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[i] Department of Hematology-Oncology, National University Cancer Institute, Singapore
[j] Department of Otolaryngology-Head and Neck Surgery, National University Hospital, Singapore
[k] Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore

ARTICLE INFO

Article history:
Received 30 March 2021
Received in revised form 8 April 2021
Accepted 9 April 2021

Keywords:
Hydroxychloroquine
Povidone-iodine
Zinc
Vitamin C
Ivermectin
SARS-CoV-2

ABSTRACT

Background: We examined whether existing licensed pharmacotherapies could reduce the spread of coronavirus disease 2019 (COVID-19).
Methods: An open-label parallel randomized controlled trial was performed among healthy migrant workers quarantined in a large multi-storey dormitory in Singapore. Forty clusters (each defined as individual floors of the dormitory) were randomly assigned to receive a 42-day prophylaxis regimen of either oral hydroxychloroquine (400 mg once, followed by 200 mg/day), oral ivermectin (12 mg once), povidone-iodine throat spray (3 times/day, 270 μg/day), oral zinc (80 mg/day)/vitamin C (500 mg/day) combination, or oral vitamin C, 500 mg/day. The primary outcome was laboratory evidence of SARS-CoV-2 infection as shown by either: (1) a positive serologic test for SARS-CoV-2 antibody on day 42, or (2) a positive PCR test for SARS-CoV-2 at any time between baseline and day 42.
Results: A total of 3037 asymptomatic participants (mean age, 33.0 years; all men) who were seronegative to SARS-CoV-2 at baseline were included in the primary analysis. Follow-up was nearly complete (99.6%). Compared with vitamin C, significant absolute risk reductions (%, 98.75% confidence interval) were observed for oral hydroxychloroquine (21%, 2–42%) and povidone-iodine throat spray (24%, 7–39%). No statistically significant differences were observed with oral zinc/vitamin C combination (23%, –5 to +41%) and ivermectin (5%, –10 to +22%). Interruptions due to side effects were highest among participants who received zinc/vitamin C combination (6.9%), followed by vitamin C (4.7%), povidone-iodine (2.0%), and hydroxychloroquine (0.7%).
Conclusions: Chemoprophylaxis with either oral hydroxychloroquine or povidone-iodine throat spray was superior to oral vitamin C in reducing SARS-CoV-2 infection in young and healthy men.

Introduction

Until mass-vaccination is successfully implemented globally, non-pharmacological interventions (NPIs) are the only proven

DOI of original article: http://dx.doi.org/10.1016/j.ijid.2021.04.045
* Corresponding author at: Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Level 10, NUHS Tower Block, 1E Kent Ridge Road, 119228, Singapore.
E-mail address: raymond_seet@nus.edu.sg (R.C.S. Seet).

http://dx.doi.org/10.1016/j.ijid.2021.04.035

measures to mitigate transmission of COVID-19 (Lee et al., 2020; Sun et al., 2020; Chen et al., 2020; Wiersinga et al., 2020). Stringent measures have been imposed by most countries to restrict physical movements, including closing borders, schools, restaurants, bars, and religious services, while targeted quarantine limits movement of identified contacts (Lee et al., 2020; Sun et al., 2020; Chen et al., 2020). Notwithstanding, the outbreak has been challenging to contain, as new case clusters continued to emerge and even surged in numbers even after the initial quarantine measures. A pharmacological agent effective in preventing COVID-19 would be a useful adjunct to NPIs, especially in a setting of uncontrolled transmission. Two anti-parasitic drugs (hydroxychloroquine (Yao et al., 2020; Liu et al., 2020; Rakedzon et al., 2021) and ivermectin (Rakedzon et al., 2021; Caly et al., 2020)) have been shown to reduce the affinity of SARS-CoV-2 to the angiotensin-converting-enzyme 2 receptors in vitro. Hydroxychloroquine inhibits SARS-CoV-2 infection of Vero cells by elevating endosomal pH (Yao et al., 2020; Liu et al., 2020), while ivermectin binds to Impα/β1 heterodimer to inhibit SARS-CoV-2 replication (Caly et al., 2020). The antiseptic povidone-iodine has immediate virucidal effects against SARS-CoV-2 (Anderson et al., 2020; Frank et al., 2020), while zinc inhibits replication of at least six coronaviruses (including SARS-CoV and others that cause common colds) (te Velthuis et al., 2010; Hunter et al., 2020). Despite a lack of preclinical evidence of efficacy against coronaviruses, vitamin C is a widely used remedy during this pandemic (Feyaerts and Luyten, 2020).

Beginning April 2020, Singapore witnessed a surge in COVID-19 cases following widespread outbreaks in residential dormitories of migrant workers, prompting strict lockdown measures to contain virus transmission and reduce spillover into the general population (Chen et al., 2020; Koh, 2020; Tan et al., 2020a; Tan et al., 2020b; Yi et al., 2020). As of 5 March 2021, more than 90% of 59,998 reported cases in Singapore involved migrant workers (Singapore Ministry of Health, 2020). Efforts to isolate and quarantine infected workers have been challenging given the high population density in the dormitories (Liu et al., 2020; Koh, 2020). We hypothesized that at least one pharmacologic agent (hydroxychloroquine, ivermectin, povidone-iodine, zinc/vitamin C combination, or vitamin C) could be efficacious as prophylaxis against SARS-CoV-2 among individuals living in a closed and high exposure setting.

Methods

Trial design and oversight

This study was an open-label, parallel randomized clinical trial to evaluate the efficacy of oral hydroxychloroquine, oral ivermectin, povidone-iodine throat spray, oral zinc/vitamin C combination, and oral vitamin C for SARS-CoV-2 prophylaxis. Subjects were randomized in clusters, with each cluster defined by the residential floor of a multi-story dormitory complex. Assigning a single intervention per floor aligned the recruitment workflow with stringent floor level movement restrictions and medication instructions to prospective participants, thereby minimizing the possibility of medication errors given the scale and timeliness of recruitment. By contrast, an individual randomization method would require five different medications to be dispensed at the same time, which could lead to medication errors and exchanges within rooms and floors. The open-label trial design was chosen as a pragmatic decision given the different routes of administration (oral vs. throat spray) and medication schedule (single dosing, once daily and twice daily) of the study prophylaxis.

Furthermore, an effective prophylactic regimen might also reduce SARS-CoV-2 transmission among residents of the same dormitory floor. At the time of trial registration, there were no approved serological tests for confirmation of SARS-CoV-2 infection. When these became available, the main secondary endpoint was upgraded to the primary endpoint to replace symptom-based endpoints (Supplementary Materials). The trial was approved by the Domain-Specific Review Board, National Healthcare Group (2020/00561), the Ministry of Health, the multi-ministerial Joint Task Force, and was conducted under a Clinical Trial Authorization (CTA2000053) by the Health Sciences Authority, which oversees all clinical trials in Singapore.

Participants

All dormitory residents aged between 21 and 60 who were willing to adhere to the study protocol, return for a review 42-days later, and provide daily symptom feedback through a mobile application, were invited to participate in this trial. Participants were excluded if they had symptom(s) of respiratory illnesses (fever, cough, runny nose, sore throat and/or shortness of breath), dysgeusia or anosmia in the past one month, had a previous diagnosis of COVID-19, or met other exclusion criteria (Supplementary Materials).

Setting

Recruitment was performed at Tuas South Dormitory, Singapore. The dormitory complex contains five residential buildings, each with nine floors and an equal number of rooms per floor; not all rooms were fully occupied during the study. Each room is divided into different sections housing double-decker beds, communal dining, wash areas, and two en suite shared bathrooms. At capacity, up to fourteen men could reside in the larger rooms (approx. 72 sq m) and up to ten men in the smaller rooms (approx. 60 sq m) (maximum density, 5.15–6.00 sq m per person). The outbreak in this dormitory was part of a larger outbreak involving migrant workers in Singapore linked to a large supermarket frequented by these workers (Tan et al., 2020b). Unlinked cases were detected sporadically in different blocks and floors with no discernable pattern, and the index case(s) could not be epidemiologically identified in this dormitory. The dormitory was gazetted as an isolation area under Singapore's Infectious Diseases Act on 23 April 2020 after the first case was identified at Tuas South Dormitory on 7 April 2020.

Enrollment into the trial began on 18 May 2020, and a recruitment window of fourteen days was set to include as many uninfected participants as possible. As part of enhanced surveillance, dormitory residents were all closely monitored and underwent nasopharyngeal swabs for SARS-CoV-2 PCR whenever they developed respiratory symptoms or were roommates of those with respiratory symptoms to facilitate early isolation (Young et al., 2020). A medical team (comprising doctors and nurses) was present on-site daily to attend to the medical needs of the dormitory residents and to perform nasopharyngeal swabs throughout the quarantine. On the day of first enrollment, 346 PCR positive cases were identified and transferred to off-site isolation facilities. As part of gazetting regulations, resident movements were strictly restricted by law. Interactions among residents living in different rooms, floors, and blocks were not permitted; these measures were reinforced by barriers placed between blocks and 24/7 security personnel. Residents were not permitted to leave the dormitories except for medical care under escort, and shared cooking facilities were closed. Food was individually packed and catered to their dietary preferences, with utensils provided with instructions not to share utensils. One representative from each room would collect individually packed food three times daily at assigned schedules. NPIs enforced included mandatory mask-wearing and regular messaging

encouraging social distancing, hand hygiene, and environmental cleaning. Within rooms, residents were asked to wear masks and encouraged to frequently wash their hands, although these measures were not enforceable within rooms out of sight of security personnel. These measures continued throughout the study period. The trial was first publicized to residents a week prior to trial initiation through the public address system, room-to-room visits by study investigators, group sessions, and distribution of pamphlets containing an internet link to written and video materials explaining the trial objectives, the voluntary basis of participation and their commitments as trial participants. The materials were available in English and other more common vernacular languages used by the migrant workers (Bengali, Burmese, Chinese, and Tamil).

On the day of recruitment, the contents of the informed consent form were read and explained in English and the worker's native languages by trained interpreters before written informed consent was obtained from individual participants. Information on demography (age and gender), country of origin, and medical history were obtained by direct interview and entered using FormSG, an encrypted tool developed by Singapore's GovTech Data Science & Artificial Intelligence Capability Centre. Body weight, height, blood pressure, and heart rate were measured in all participants. Each room was graded according to the risk of SARS-CoV-2 exposure; unexposed rooms had no identified confirmed COVID-19 cases at any time before randomization. Participants were asked to report their symptoms daily using Form SG. Each participant was given a mobile number to contact the study team by phone call or SMS throughout the study. In consultation with the Singapore regulators, additional safety measures were added following adverse safety reports arising from the use of hydroxychloroquine for COVID-19 treatment (Mehra et al., 2020). A 12-lead electrocardiogram was performed in all participants randomized to receive hydroxychloroquine. Participants with the following electrocardiogram and blood pressure/heart rate findings were excluded from hydroxychloroquine prophylaxis: corrected QT interval exceeding 450 ms, any arrhythmia (including benign ones, e.g., premature atrial or ventricular complexes), left ventricular hypertrophy, left bundle branch block, systolic blood pressure >140 mmHg, diastolic blood pressure >85 mmHg and heart rate >100 per min.

Blood samples were collected from all participants at randomization, and 42 days later, extracted sera were analyzed for antibody response to SARS-CoV-2 using the Elecsys® anti-SARS-CoV-2 antibody test (Roche, Germany). Results of participants who underwent nasopharyngeal swabs for SARS-CoV-2 RNA detection by quantitative RT-PCR method (Young et al., 2020) were retrieved from medical records to ascertain the status of SARS-CoV-2 infection.

Interventions

After randomization, each participant was supplied with a 42-day supply of the assigned intervention (except for ivermectin that was administered as a single dose) and was responsible for taking the medication as instructed without further direct supervision or observation by the study team. Hydroxychloroquine was sourced as hydroxychloroquine sulfate from Shanghai Pharmaceuticals Holding Co., Ltd in 100 mg tablets, ivermectin from Edenbridge Pharmaceuticals LLC as 3 mg tablets, povidone-iodine as povidone-iodine 0.45% (Betadine®) from Mundipharma Pte Ltd, zinc was sourced as zinc oxide 40 mg in combination with vitamin C 250 mg (Macu-Vision®) from Blackmores Ltd and vitamin C in 500 mg tablets also from Blackmores Ltd. The dosing regimen of hydroxychloroquine sulfate was 400 mg (four tablets) once, followed by 200 mg (two tablets) daily for 42 days. Although pharmacokinetic studies suggested a higher dosage of ivermectin (50- to 100-fold higher than approved limits) may be necessary to inhibit SARS-CoV-2 replication (Caly et al., 2020), sparse human data are available to support the safety and efficacy of ivermectin against SARS-CoV-2 at these doses. Given these uncertainties, we kept the dosage of ivermectin to within the approved limits of 200 μg/kg; a single dose of 12 mg was administered in participants who weighed >60 kg. Povidone-iodine throat spray was self-administered three times daily (approximately 270 μg/day) for 42 days. Zinc (40 mg) was administered in combination with vitamin C (250 mg) twice daily (total, zinc 80 mg and vitamin C 500 mg/day), while Vitamin C (500 mg) was administered once daily. The first dose of hydroxychloroquine (400 mg) or ivermectin (12 mg) was consumed in the presence of the study team. On day 42, participants were asked to grade their medication adherence on a score of 0–10 (where 0 = non-adherence and 10=full adherence), which was verified by counting the number of remaining pills. Temasek Foundation, a Singapore-based philanthropic organization, donated hydroxychloroquine and ivermectin, Mundipharma Pte Ltd donated the povidone-iodine throat spray, while Blackmores Ltd donated zinc/vitamin C and vitamin C tablets used in this study. None of these organizations had any input into the study design or analysis.

Outcomes

The primary outcome was laboratory-confirmed SARS-CoV-2 infection as shown by either: (1) a positive serologic test for SARS-CoV-2 antibody on day 42, or (2) a positive PCR test for SARS-CoV-2 at any time between baseline and day 42. Secondary outcomes were acute respiratory symptoms (defined by the presence of any of the following symptoms: fever, cough, shortness of breath, sore throat, runny nose, or change in smell/taste), symptomatic infection, and pneumonia requiring hospitalization. Symptomatic infection refers to the presence of acute respiratory symptoms in the presence of laboratory-confirmed SARS-CoV-2 infection. Post-hoc survival analyses were performed to compare the incidence of SARS-CoV-2 infection between each intervention group using SARS-CoV-2 RNA swab positivity data.

Sample size calculation

The original sample size calculation was based on individual randomization, which prioritized the number of participants. We had initially estimated a sample size of 550 subjects would need to be enrolled in each prophylaxis arm to detect a 20% difference between intervention and control groups with a power of 80% and $\alpha = 0.0125$ (adjusted for multi-intervention comparisons by Bonferroni's methods). By assuming 10% seropositivity at baseline and a 10% rate of attrition, we projected a minimum sample size of 660 participants per arm. These calculations, however, did not consider cluster randomization, which was the only practical option based on the situation on the ground. Using sample size that was initially projected per arm based on the expected effect, eight clusters per arm (as the number of floors available for randomization was fixed) with cluster sizes of 75 subjects, and an intracluster correlation of $\rho = 0.1$ (as observed in the actual study), the retrospective power of the study to detect an absolute difference in risk of 0.3 was ~70%; the conditional power for povidone-iodine and hydroxychloroquine versus vitamin C was 99% and 85%, respectively (Supplementary materials).

Randomization

Each room was ordered sequentially numbered by block and floor and imported into statistical computer software Stata V.16,

which randomly allocated floors to interventions and control prior to study initiation. Information on cluster allocation was concealed by a study statistician who informed the study team of the assigned intervention and floor a day before recruitment to facilitate preparations.

Statistical methods

We excluded those seropositive at baseline. We assessed laboratory-confirmed SARS-CoV-2 infection between intervention groups using logistic regression methods with random effects to accommodate clustering, deriving derived odds ratios (with 98.75% confidence intervals to accommodate multiple testing) and Wald p-values. Bootstrap 98.75% confidence intervals for the absolute and relative risk differences compared to Vitamin C were derived by bootstrapping at the cluster-level. In the secondary analysis, we adjusted for exposure to cases in the same room at the point of recruitment, as this modulated the risk in exploratory analysis. Cumulative incidence of SARS-CoV-2 infection across time was assessed using PCR-confirmed infection that occurred before the end of active follow-up. Those without a PCR test or with a negative PCR but who continued in the study, were censored at the end of active follow-up, approximately 42 days after enrollment, when serology was taken, or until an event occurred. Otherwise, the individual was censored at the end of active follow-up. To address multiple testing arising from having four other intervention arms that we compared against Vitamin C, a Bonferroni-corrected level of α = 0.0125 was used to determine statistical significance. All statistical analyses used R (R Core Team, 2020).

Results

Recruitment of primary cohort

Of the 45 available floors, three floors were repurposed as dedicated isolation facilities for identified cases before they were relocated off-site for appropriate care; the remaining 42 floors ("clusters") were available for randomization. Of these, 40 floors were randomly selected and assigned in equal ratios to receive the trial interventions (Fig. 1). Two floors were reserved to balance the sample size in each prophylaxis arm; these contingency measures were necessary as there were initial uncertainties on the residents' willingness to participate in a clinical trial. To achieve the sample size targets, men from these two non-randomized floors were recruited into the different arms, and those who did not fulfill the bodyweight criteria for ivermectin and the blood pressure and heart rate criteria for hydroxychloroquine were assigned to receive vitamin C. A total of 5255 out of 6502 men residing in the dormitory were evaluated for study eligibility; 1247 men declined to participate. A total of 998 men were excluded as they did not meet the eligibility criteria (Fig. 1). Of the 4257 men who were recruited, data from 849 men who were recruited from non-randomized floors (including those who received vitamin C but recruited from hydroxychloroquine and ivermectin-assigned floors) (Supplementary Materials, Table S1) and men who were found to be seropositive to SARS-CoV-2 on recruitment (n = 359) were excluded from the primary analysis. Baseline seropositive rates per cluster were hydroxychloroquine 10.0%, ivermectin 12.4%, povidone-iodine 14.5%, zinc/vitamin C 8.1% and vitamin C 6.3%. Twelve men withdrew, and 3037 men completed the 42-day study (retention rate 99.6%).

The primary cohort comprised 3037 men (mean age, 33.0 years, mostly from India and Bangladesh) who received hydroxychloroquine (n = 432), ivermectin (n = 617), povidone-iodine (n = 735), zinc/vitamin C combination (n = 634), and vitamin C (n = 619) (Table 1). A total of 42 (1.4%) men reported chronic health conditions, with hypertension being the most common (1.0%), followed by diabetes mellitus (0.3%) and hyperlipidemia (0.1%), while 2009 (66.2%) men resided in rooms with no prior exposure to known COVID-19 individuals. Although 653 men were initially assessed from hydroxychloroquine-assigned floors, 172 were excluded after meeting blood pressure and heart rate (n = 162) and EKG exclusion criteria (n = 10; premature ventricular, n = 8, and atrial complexes, n = 2).

Primary outcome

Laboratory-confirmed SARS-CoV-2 infection was diagnosed in 1681 of 3037 (55.4%) men. The frequency of SARS-CoV-2 infection was significantly lower in participants receiving hydroxychloroquine (212 out of 432 participants, 49%) and povidone-iodine throat spray (338 out of 735 participants, 46%), compared with vitamin C (433 out of 619 participants, 70%). Based on alpha = 0.0125 (to account for multiple comparisons), no statistically significant differences were observed between zinc/vitamin C (300 out of 634 participants, 47%) and ivermectin (398 out of 617 participants, 64%), compared with vitamin C (Table 2). Compared with vitamin C, significant absolute risk reductions (%, 98.75% confidence interval) were observed for oral hydroxychloroquine (21%, 2–42%) and povidone-iodine throat spray (24%, 7–39%) (Table 3). No statistically significant absolute risk reductions were observed with zinc/vitamin C combination (23%, −5 to +46%) and ivermectin (5%, −10 to +22%). Reduction in the incidence of SARS-CoV-2 infection in the hydroxychloroquine and povidone-iodine throat spray groups remained statistically significant after adjustments were made for potential confounders (previous room exposure, age categories, nationalities, compliance to medications, and baseline seropositivity within the same cluster) (Table 4). Although younger age and Indian nationals had statistically lower infection rates (Supplementary Materials, Table S2), including age and nationality had almost no impact on the odds of infection in each arm.

Secondary outcomes

A total of 201 (6.6%) men reported acute respiratory symptoms during the trial. Despite no evidence of their having lower infection rates, men who received ivermectin had fewer symptomatic infections compared with vitamin C (Table 2). No pneumonia requiring hospitalization or death occurred. A total of 309 men had COVID-19 diagnosed by SARS-CoV-2 RNA detection from nasopharyngeal swabs, thereby allowing for post-hoc time-based analysis between SARS-CoV-2 infection and intervention groups. There was no evidence of a statistically significant difference between arms in the timing of infections (Table S3 and Fig. S1) after accounting for clustering, though the direction and magnitude of effect sizes were consistent with the primary endpoint. To interrogate the primary outcome further, additional analyses were performed to investigate the potential impact of medication adherence on SARS-CoV-2 infection according to the different groups. Consistently, men with greater medication adherence were significantly less likely to be infected (Supplementary materials, Table S4, and Fig. S2).

Adherence and safety

Adherence among the trial participants was moderately good, with 80% grading their adherence as 7 or more (on a scale of 10). Apart from the ivermectin group (where the intake was directly observed), adherence was highest in the povidone-iodine group (88%) and lowest in the hydroxychloroquine group (71%) (Table 5).

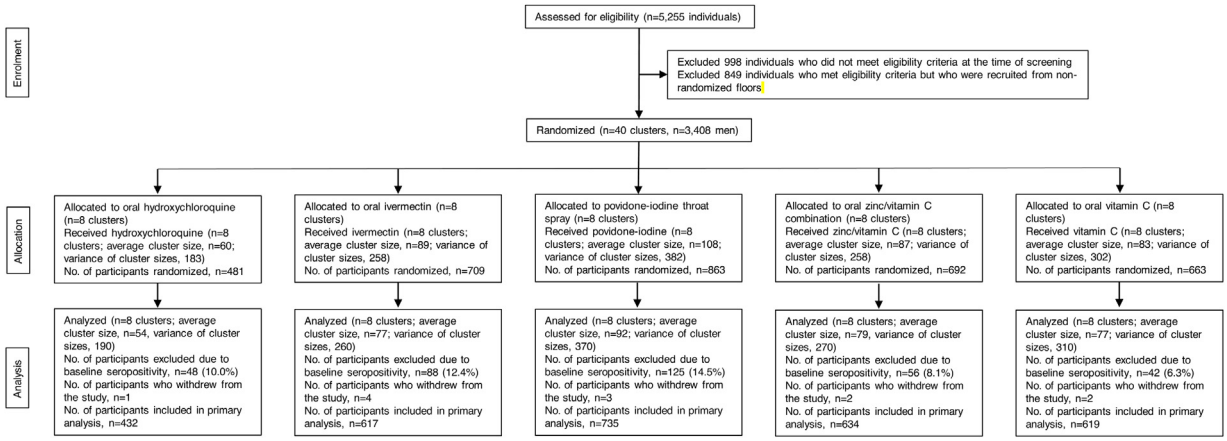

Fig. 1. Screening and randomization.
Of the 5255 individuals assessed for eligibility, 998 did not meet the eligibility criteria at the time of screening and were excluded. A further 849 individuals who met the eligibility criteria were excluded as they were recruited from non-randomized floors; participants from hydroxychloroquine and ivermectin assigned floors who met additional study exclusions and received vitamin C formed part of the 849 excluded individuals. Overall, 40 clusters were randomized in equal ratios to receive the different interventions, involving 3408 men. In the hydroxychloroquine arm, 48 were excluded due to baseline seropositivity, and one withdrew from the study; data from the remaining 432 participants who received hydroxychloroquine were included in the primary analysis. In the ivermectin arm, 88 were excluded due to baseline seropositivity, and four participants withdrew from the study; the remaining 617 participants were included in the primary analysis for ivermectin. Of the 863 randomized participants in the povidone-iodine arm, 125 were excluded due to baseline seropositivity; three participants withdrew from the study; the remaining 735 participants were included in the primary analysis for povidone-iodine. In the zinc/vitamin C arm, of the 692 randomized participants, 56 were excluded due to baseline seropositivity, and two participants withdrew from the study; the remaining 634 participants were included in the primary analysis for zinc/vitamin C. In the vitamin C arm, of the 663 randomized participants, 42 were excluded due to baseline seropositivity, and two participants withdrew from the study; the remaining 619 participants were included in the primary analysis for vitamin C.

Table 1
Study participants.

	Hydroxychloroquine N = 432	Ivermectin N = 617	Povidone-iodine N = 735	Zinc & vitamin C N = 634	Vitamin C N = 619
Participant characteristics					
Age (y), mean (SD)	30.6 (6.4)	33.6 (6.9)	32.0 (6.6)	33.2 (7.8)	32.9 (7.1)
Country of origin					
Bangladesh	166 (38.4%)	324 (52.5%)	259 (35.2%)	305 (48.1%)	288 (46.5%)
India	265 (61.3%)	256 (41.5%)	474 (64.5%)	327 (51.6%)	320 (51.7%)
Others	1 (0.2%)	37 (6.0%)	2 (0.3%)	2 (0.3%)	11 (1.7%)
No room exposure[a]	293 (67.8%)	378 (61.3%)	482 (65.6%)	457 (72.1%)	399 (64.5%)
Medical history					
Hypertension	2 (0.5%)	8 (1.3%)	3 (0.4%)	12 (1.9%)	3 (0.5%)
Diabetes mellitus	1 (0.2%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	2 (0.3%)
Hyperlipidemia	0	3 (0.5%)	0	1 (0.2%)	0
Baseline parameters					
Systolic BP (mmHg)	123.8 (11.3)	132.8 (15.1)	130.2 (15.0)	130.1 (16.6)	128.4 (16.1)
Diastolic BP (mmHg)	79.2 (6.9)	86.7 (10.0)	84.8 (10.7)	86.3 (11.0)	84.5 (10.7)
Pulse rate (per min)[b]	86.5 (9.3)	92.6 (12.2)	92.9 (13.5)	89.9 (13.7)	90.9 (12.9)
Body mass index (kg/m^2)	23.2 (3.2)	25.2 (2.7)	23.8 (3.5)	24.2 (3.5)	24.0 (3.2)

Age and country of origin were verified with their employment identification documents; other countries of origin included China, Malaysia, Myanmar, the Philippines and Thailand.
[a] Denotes number (%) of participants living in rooms that never had anyone diagnosed with COVID-19 at the time of randomization.
[b] Denotes resting heart rate.

Interruptions due to side effects were highest among men who received zinc/vitamin C combination (6.9%), followed by vitamin C (4.7%), povidone-iodine (2.0%), and hydroxychloroquine (0.7%). The lower adherence to hydroxychloroquine was attributed mainly to concerns of potential side effects (12%) and personal decisions (3%) than for actual side effects. Men in the povidone-iodine group were least symptomatic (14%) compared with the other interventions (hydroxychloroquine 20%, ivermectin 22%, zinc/vitamin C combination 18% and vitamin C 20%, p = 0.003); fewer in the povidone-iodine group complained of headaches, loss of appetite and constipation (Table 4). Among men who received hydroxychloroquine, corrected QT interval did not statistically significantly differ between baseline and follow-up readings (mean, 379 vs. 378 ms, respectively; paired t-test, p = 0.387).

Discussion

In this open-label randomized clinical trial, short-term use of either oral hydroxychloroquine or povidone-iodine throat spray was found to be superior to vitamin C in lowering the incidence of laboratory-confirmed SARS-CoV-2 infection among men living in a closed and high exposure setting. In contrast, SARS-CoV-2 infection did not statistically significantly differ between men who received oral zinc and vitamin C combination and a single

Table 2
Primary and secondary outcomes.

	Hydroxychloro-quine		Ivermectin		Povidone-iodine		Zinc & vitamin C		Vitamin C
	N = 432	P-value	N = 617	P-value	N = 735	P-value	N = 634	P-value	N = 619
Primary outcome									
Laboratory-confirmed SARS-CoV-2 infection	212 (49.1%)	0.011*	398 (64.5%)	0.50	338 (46.0%)	0.011*	300 (47.3%)	0.033	433 (70.0%)
Seropositive	179	0.058	308	0.56	288	0.073	250	0.12	348
RNA positive	32	0.10	90	0.97	50	0.054	50	0.14	85
Secondary outcomes									
Acute respiratory symptoms	31 (7.2%)	0.14	35 (5.7%)	0.012*	43 (5.9%)	0.054	34 (5.4%)	0.029	69 (11.1%)
Symptomatic COVID-19	29/212 (13.7%)	0.80	32/398 (8.0%)	0.0034*	42/338 (12.4%)	0.41	33/300 (11.0%)	0.17	64/433 (15.0%)
Pneumonia requiring hospitalization	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)
Deaths	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)	–	0 (0%)

P-values are for comparison versus vitamin C arm. For primary outcomes and acute respiratory symptoms, p-values adjust for clustering through random effects logistic regression. Respiratory symptoms are defined by any of the following symptoms: fever, cough, shortness of breath, sore throat, runny nose, or change in smell/taste. P-values significant at a Bonferroni-corrected level of 0.0125 are starred. Quantities are number (%) unless otherwise specified.

Table 3
Absolute risk reduction and relative risk in incident SARS-CoV-2 infection between the different interventions and comparator (vitamin C). Confidence intervals are bootstrap intervals using each cluster (residential level) as the sampling unit. The Bonferroni corrected alpha is 0.0125; Confidence intervals are calculated at 98.75% to match the Bonferroni corrected alpha.

Arm	Infected (N)	Total (N)	SARS-CoV-2 positivity (%, 98.75%CI)	Absolute risk reduction (%, 98.75%CI)	Relative risk (ratio, 98.75%CI)
Vitamin C	433	619	70 (57, 81)	Reference	Reference
Hydroxychloroquine	212	432	49 (31, 62)	21 (2, 42)	0.70 (0.44, 0.97)
Ivermectin	398	617	65 (51, 73)	5 (−10, 22)	0.93 (0.71, 1.18)
Povidone-iodine	338	735	46 (35, 56)	24 (7, 39)	0.66 (0.48, 0.88)
Zinc and Vitamin C	300	634	47 (27, 72)	23 (−5, 46)	0.67 (0.38, 1.08)

Table 4
Adjusted odds ratios (aOR) in incident SARS-CoV-2 infection between the different interventions and comparator (vitamin C) with and without adjusting for confounders. Random effects at the cluster level are included together with fixed effects for the tabulated variables. Model 1 incorporates each cluster as a random effect within a mixed effect logistic regression. Model 2 additionally includes exposure at the beginning of the trial. The Bonferroni corrected alpha is 0.0125; tests significant at that level are starred. Confidence intervals are calculated at 98.75% to match the Bonferroni corrected alpha. Model 3 accounts for age group; Model 4 for nationality, Model 5 for compliance to medication; and Model 6 for baseline seroprevalence among other men in the same cluster. Confidence intervals are obtained through adaptive Gauss-Hermite quadrature to integrate over the space of random effects; p-values are derived from asymptotic Wald tests under the assumption that the likelihood surface is approximately Gaussian. These assumptions differ and thus the p-values and confidence intervals are not wholly in agreement.

Arms	Model 1 aOR (98.75% CI)	p	Model 2 aOR (98.75% CI)	p	Model 3 aOR (98.75% CI)	p	Model 4 aOR (98.75% CI)	p	Model 5 aOR (98.75% CI)	p	Model 6 aOR (98.75% CI)	p
Vitamin C	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Hydroxychloroquine	0.37 (0.13, 1.01)	0.011*	0.37 (0.14, 0.98)	0.0085*	0.38 (0.14, 1.00)	0.0099*	0.38 (0.14, 1.01)	0.011*	0.34 (0.12, 0.92)	0.0052*	0.39 (0.15, 0.99)	0.0094*
Ivermectin	0.77 (0.27, 2.14)	0.50	0.74 (0.27, 2.00)	0.44	0.73 (0.27, 1.96)	0.41	0.73 (0.27, 1.98)	0.41	0.89 (0.32, 2.48)	0.78	0.83 (0.32, 2.15)	0.61
Povidone-iodine	0.37 (0.13, 1.02)	0.011*	0.36 (0.13, 0.97)	0.0073*	0.36 (0.13, 0.96)	0.0068*	0.37 (0.14, 1.00)	0.0097*	0.38 (0.14, 1.03)	0.012*	0.40 (0.15, 1.03)	0.012*
Zinc and Vitamin C	0.43 (0.15, 1.20)	0.033	0.42 (0.16, 1.15)	0.026	0.42 (0.15, 1.13)	0.022	0.42 (0.15, 1.15)	0.025	0.42 (0.15, 1.16)	0.027	0.45 (0.17, 1.19)	0.032
Variables												
Previous room exposure	–	–	1.42 (1.13, 1.78)	0.00012*	1.42 (1.13, 1.78)	0.00013*	1.38 (1.10, 1.74)	0.0004*	1.39 (1.10, 1.76)	0.0005*	1.44 (1.14, 1.80)	<0.0001*
Age <30	–	–	–	–	1.00 (reference)	–	–	–	–	–	–	–
Age 30–39	–	–	–	–	1.20 (0.97, 1.50)	0.036	–	–	–	–	–	–
Age 40–49	–	–	–	–	1.40 (1.03, 1.92)	0.0062*	–	–	–	–	–	–
Age 50–59	–	–	–	–	1.17 (0.54, 2.58)	0.62	–	–	–	–	–	–
Bangladeshi	–	–	–	–	–	–	1.00 (reference)	–	–	–	–	–
Indian	–	–	–	–	–	–	0.78 (0.63, 0.98)	0.0056*	–	–	–	–
Neither Indian nor Bangladeshi	–	–	–	–	–	–	0.99 (0.47, 2.19)	0.97	–	–	–	–
High compliance to medication	–	–	–	–	–	–	–	–	0.56 (0.43, 0.73)	<0.0001*	–	–
Baseline seropositivity (%) in the same cluster	–	–	–	–	–	–	–	–	–	–	0.98 (0.95, 1.01)	0.05

Table 5
Participant-reported adherence and side effects.

	Hydroxychloroquine	Ivermectin	Povidone-iodine	Zinc & vitamin C	Vitamin C	P Value
Reported >70% adherence to trial intervention – no. (%)[a]	292/409 (71.4%)	572/572 (100%)	623/707 (88.1%)	471/610 (77.2%)	463/579 (80.0%)	<0.001
Reasons for suboptimal adherence to trial intervention - no. (%)[a]						<0.001
Developed side effects	3 (0.7%)	–	15 (2.0%)	44 (6.9%)	29 (4.7%)	
Concerns of side effects	53 (12.2%)	–	11 (1.5%)	15 (2.4%)	20 (3.2%)	
Personal decision to reduce or stop intervention	14 (3.2%)	–	13 (1.8%)	29 (4.6%)	16 (2.6%)	
Thinks intervention does not work	1 (0.2%)	–	1 (0.1%)	0	0	
Advised not to take by friends or family	3 (0.7%)	–	1 (0.1%)	3 (0.5%)	0	
Developed COVID-19	9 (2.1%)	–	11 (1.5%)	14 (2.2%)	25 (4.0%)	
Symptom surveillance of participants who started trial interventions – no./total no. (%)[b]	N = 413	N = 605	N = 703	N = 579	N = 563	
Any	82 (19.9%)	132 (21.8%)	98 (13.9%)	106 (18.3%)	115 (20.4%)	0.003
Headaches	39 (9.4%)	62 (10.2%)	42 (6.0%)	41 (7.1%)	53 (9.4%)	0.029
Loss of appetite	14 (3.4%)	32 (5.3%)	13 (1.8%)	14 (2.4%)	32 (5.7%)	<0.001
Constipation	13 (3.1%)	25 (4.1%)	17 (2.4%)	17 (2.9%)	34 (6.0%)	0.009
Increased sleepiness	30 (7.3%)	23 (3.8%)	35 (5.0%)	30 (5.2%)	23 (4.1%)	0.117
Skin reaction	15 (3.6%)	24 (4.0%)	19 (2.7%)	19 (3.3%)	22 (3.9%)	0.717
Body aches	14 (3.4%)	21 (3.5%)	19 (2.7%)	12 (2.1%)	23 (4.1%)	0.330
Chest pain	5 (1.2%)	16 (2.6%)	13 (1.8%)	6 (1.0%)	11 (2.0%)	0.258
Nausea, vomiting	2 (0.5%)	8 (1.3%)	6 (0.9%)	6 (1.0%)	7 (1.2%)	0.698
Joint pain	7 (1.7%)	6 (1.0%)	8 (1.1%)	4 (0.7%)	9 (1.6%)	0.534
Stomach pain	8 (1.9%)	14 (2.3%)	11 (1.6%)	9 (1.6%)	8 (1.4%)	0.767
Mood changes	6 (1.5%)	10 (1.7%)	8 (1.1%)	11 (1.9%)	9 (1.6%)	0.856
Diarrhea	7 (1.7%)	4 (0.7%)	7 (1.0%)	6 (1.0%)	6 (1.1%)	0.634
Chest tightness	5 (1.2%)	10 (1.7%)	12 (1.7%)	5 (0.9%)	8 (1.4%)	0.721
Palpitations	6 (1.5%)	6 (1.0%)	4 (0.6%)	6 (1.0%)	6 (1.1%)	0.691

[a] Medication adherence was assessed in participants during the final visit using an objective adherence score that was verified by counting the remaining pills, and compared between intervention groups. Participants who were isolated in outside facilities after being diagnosed with COVID-19 and who were not able to reproduce the medication package for pill-counting were excluded from adherence analysis. Reasons for suboptimal adherence was collected from participants who reported <70% adherence to trial prophylaxis.

[b] Information on side effects was collected by surveying daily symptoms of participants during the 42-day trial using a FormSG mobile application. Participants who were not present during the final visit and who reported <30% times in their symptom diary were excluded from side effect analysis.

dose of ivermectin compared with vitamin C. This study addressed the limitations of previous studies (Boulware et al., 2020; Abella et al., 2020; Mitjà et al., 2020) by incorporating serological and molecular assays without relying on subjective symptom-reporting and by following participants for a longer duration of 42 days. Ascertaining diagnosis using laboratory methods ensures the primary outcome is not vulnerable to reporting biases and allows characterization of participants who remained asymptomatic or pauci-symptomatic throughout infection (Wiersinga et al., 2020; Li et al., 2020; Nikolai et al., 2020). Prevention of infections from asymptomatic and symptomatic individuals is central to halting the spread of the virus as they are both known to transmit infection.

Our findings contrast with data from recent randomized trials (Boulware et al., 2020; Abella et al., 2020; Mitjà et al., 2020), primate studies (Maisonnasse et al., 2020) and in vitro studies using human cell lines (Hoffmann et al., 2020) that suggested a lack of efficacy of hydroxychloroquine for SARS-CoV-2 prevention. In this study, a significant reduction in SARS-CoV-2 infection was observed in men who received a lower daily dose of hydroxychloroquine but over a more prolonged period of 42 days. It is unclear whether these discrepant findings could be partly explained by a delay in initiating prophylaxis in previous studies (up to six days following a self-reported exposure), which did not allow hydroxychloroquine sufficient time to exert a prophylactic effect. By contrast, the more prolonged prophylaxis in the current study ensured a higher cumulative level of hydroxychloroquine was achieved. Interestingly, more men had concerns for adverse effects and were advised by their friends and family members to discontinue hydroxychloroquine despite experiencing fewer adverse events. Consistent with previous trials (Boulware et al., 2020; Abella et al., 2020; Mitjà et al., 2020), we did not observe clinically apparent cardiac effects that have been reported following acute treatment (Rosenberg et al., 2020; Stevenson et al., 2020; Goldman et al., 2020), or subclinical changes in electrocardiographic corrected QT measurements. However, it is also unclear whether screening out men with abnormal blood pressure or electrocardiogram would have skewed the selection of healthier men in the hydroxychloroquine group and inadvertently excluded those who might be more prone to cardiac effects of the drug. While limited in its generalizability, this study suggests that the question of the benefits of hydroxychloroquine in prophylaxis in certain settings has not yet been conclusively settled.

The study is novel in that it includes topical therapy in the form of povidone-iodine administration by throat spray, which lowered SARS-CoV-2 infection by 24% compared with vitamin C. These findings support in vitro data that suggest potent virucidal effects of povidone-iodine against SARS-CoV-2 (Anderson et al., 2020; Frank et al., 2020), potentially capable of creating a relatively resistant environment within the oropharyngeal space. Consequently, a reduction in viral load could reduce the exposure of aerosolized virus particles to their close contacts during the incubation and asymptomatic phases of infection, thereby interrupting transmission of SARS-CoV-2. Compared with other interventions, participants who received povidone-iodine throat spray reported the highest medication adherence with fewer reporting side effects and medication discontinuation than the vitamin C arm, thereby supporting their tolerability and future applications. By contrast, we did not observe differences in SARS-CoV-2 infection between participants who received zinc/vitamin C combination and a single fixed dose of 12 mg ivermectin (within the approved dose of 200 μg/kg). It remains uncertain whether a larger sample size in the zinc/vitamin C combination arm could

alter this conclusion and whether the results would differ had higher and repeated doses of ivermectin been studied.

The study has several limitations. First, we did not reflect the trial's cluster-randomized design when deriving sample sizes as the degree of clustering was unknown *a priori*, and thus probably underprojected the number of clusters and subjects needed to detect differences between intervention groups. The additional exclusion criteria in the hydroxychloroquine arm resulted in fewer eligible participants in this arm, which could undermine the balancing property of randomization between medication groups. Second, it is arguable whether vitamin C was a suitable comparator and whether a placebo pill could serve as a better control. We decided against administering placebo as this would have undermined recruitment in the placebo arm given the open-label trial design as well as the ethical legitimacy of administering placebo pills in an outbreak setting. Third, we studied only young to middle-aged men with fewer comorbidities (e.g., hypertension, hyperlipidemia, etc.) living in a dormitory, which could explain the milder disease and apparent lack of pneumonia, thereby limiting the generalizability of our findings. Fourth, despite active measures in the dormitory to enforce NPIs, we did not assess compliance with social distancing, personal hand hygiene, and mask-wearing. However, it is unlikely that a significant variation would occur as the study was performed in a single dormitory with uniform infrastructure and supplies and strict policing by security personnel. Fifth, for resource, microbiological and logistical reasons, we did not perform nasopharyngeal swabs for the entire cohort and therefore could not exclude the possibility that some participants could harbor asymptomatic infection on recruitment. However, diagnosing asymptomatic infection can be challenging as the sensitivity of quantitative PCR could be as low as 30% in asymptomatic individuals depending on whether the test is performed during the incubation, presymptomatic, or recovery phases of the disease (Dong et al., 2021; Ternovoi et al., 2020). To further improve its accuracy, repeated PCR tests may be required.

Similarly, the ability to mount an antibody response differs between individuals, and a delay in response could lead to a false-negative result. However, the impact of such variability is minimized by standardizing the timing of blood taking (baseline and day 42) across the different medication arms. Sixth, heterogeneity in exposure to infectious pathogens is difficult to control for in human trials. In this study, adjusting for different surrogates of exposure (room exposure and baseline seropositivity on the different floors) did not alter our primary findings.

Vulnerable settings where the transmission can go unchecked have been clearly identified throughout the pandemic. Implementing NPIs may be very challenging in such settings, and there is a pressing need for additional means to prevent spread. Such settings include cruise ships, prisons, refugee camps, and meat processing facilities. This is the first study to demonstrate the benefits of prophylactic therapy with either oral hydroxychloroquine or povidone-iodine throat spray in reducing SARS-CoV-2 infection among quarantined individuals living in a closed and high exposure setting. These pharmacotherapies could be used to complement existing NPIs in settings where transmission is high while awaiting the rollout of a vaccine. Further research could analyze the effects in older people and women and those with immune compromise and other significant comorbidities over more prolonged periods.

Dorm Trial Investigators

Neha Burla, Sebastiaan Zhiyong Blok, Ian Chai Jie, Chan Ching Wan, Ryan Ian Houe Chong, Corissa Yi Juan Chee, Ganga Devi Chandrasegran, Soh Eng Chew, Ying Jia Chew, Adeline Wai Lyn Chow, Bernadette Guek Chang Er, Victoria Sze Hui Goh, Su-Ann Goh, Ashley Shuen Ying Hong, Jing Jing Hong, Bushra Habib Mohd, Ting Ting Koh, Jorshall Jin Hao Law, Hui Min Lau, Lee Ying Long Xavier, Owen Ming Hao Lee, Shaun She Ern Loong, Darren Qi Ming Leong, Xin Wei Liew, Huey Ying Lim, David Zhi Wei Lim, Michael Wen Wei Leong, Jenny Liu, Nur Khaliesah Mohamed Riza, Nor Fa'izah Mahmud, Emily Pauline Nickles, Mei Yen Ng, Jia Qi Ng, Geelyn Jeng Lin Ng, Dhikshitha Nagaraj, Filzah Hanis Osman, Amanda Tze Woon Ong, Ramapatna L Satish, Sharmila Sengupta, Poh Loong Soong, Gabriel Yiqin Tham, Siew Li Tan, Tiffany Grace Wong, E-Shuen Wong, Althea Yi Xin Wee, Ashley Yew, Siok Hoon Yeo, Yen Shing Yeoh

Authors contributions

All authors have made substantial contributions to the publication. RSCS, QMLA, PAT, and MH contributed to the conception and design of the study and acquisition of data, drafted the article, revised it critically for important intellectual content, and approved the final version for submission. DSQO, SS, SRL, CYK, JBYS, BCG, KSL, DF, and HLT have contributed to the conception and design of the study and acquisition of data, revised it critically for important intellectual content, and approved the final version for submission. JS and ARC have contributed to statistical analysis, revised the manuscript for important intellectual content, and approved the final version for submission.

Conflicts of interest

Dr. Seet reported receiving grants from the National Medical Research Council and Temasek Foundation, Singapore. Dr. Tambyah reported receiving grants from Johnson and Johnson, GlaxoSmithKline, and Roche.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author. Data suppression rules apply to ensure the anonymity of the study participants.

Funding

We are grateful to the National Medical Research Council (COVID19RF2-0052,COVID19RF-004,CSA-SI/0003/2015, andCSA-SI/0015/2017), Temasek Foundation - Singapore Millennium Foundation (SMF), and National University Hospital Research Office (NUHSRO/2020/069) for their generous support.

ClinicalTrials.gov number

NCT04446104

Acknowledgements

The authors are indebted to our participants, volunteers, sponsors, the operations team at Tuas South Dormitory, Tissue Repository Unit at the National University Hospital (NUH), NUH Research Office, Dean's Office at the Yong Loo Lin School of Medicine, and funding agencies for their generous support of this study. Our volunteers (Sharmin Afroze, Aloysius, Bushra Zafreen Amin, Adhikary Aniruddha, Sharen d/o Asif, Boey Ming Yao Brian, Edmund Chan, Chang Ting Yu, Harold Chan Yu Chung, Ann-Marie Chacko, Joseph Cheng Yuen Juin, Chiew Keong, John, Chi Hong Hui, Cheah Wai Yuen, Cheryl Chua Wan Xuan, Tan Xu Da, Ei Zune The, Fong Joon Sung, Javis Fung, Sakshi Garg, Megan Goh, Vennila Gopal, Oscar Han Wei Xuan, Jayasutha Samuthiran, Kok Wai Kit, Jerome, Kim Guowei, Douglas Lai, Yap Lai Lai, Law Jia Hao, Christy Lee Whei

Lynn, Josephine Lee, Jessica Lee Yun Ning, Lim Wen Hui, Brandon Loo Yong Kiat, Lynette Mee Ann Loo, Loo Swee Chin, Caitlin Loh Yuen Ling, Chloe Hui Xuan Low, Christopher Low Jer Wei, Grace Low Jo-Ann, Jennifer Mei Chin Low, Mohammad Neamul Kabir, Ng Jun Quan, Matthew Ng Song Peng, Nwe Ni Aung, Kay Wei Ping Ng, Ong Siong Gim, Vinesha Pillai, Nageiswari Parathy, Owen Thomas Pan, R. Punitha, Kavitha Ravindan Sambhavi Rajangam, Subhasish Ray, Mallika Raguraman, Vijay Ramadoss, Sakthivel, Noah Sim Yu Ting, Arijit Shaw, Andy Song Yu Ze, Arjunan Subramanian, Darren Tan Jun Hao, Grace Tan, Nicolette Tan Wei Qi, Ron Tan Jun Yen, Lenice Tan Yue Tong, Tan Wei Yee, Brenna Tan Shi Ting, Phoebe Tay Wen Lin, Yap Qi Tian, Aparna Venkatesh, Sabine Lauren Chyi Hui Wong, Wang Rui Sheng, Wang Yuhang, Grace Xie Chunxia, Guo Yaling, Yang Hui, Jia Ying, Megan Zhuo Yanling) were instrumental to the successful recruitment and follow-up of all participants. We are grateful to Mundipharma Pte Ltd (Ho Weng Tong), Temasek Foundation (Fidah Alsagoff, Kim Png, Shruthi Kumar), and Blackmores Ltd (Francine Tay, Claire Briggs, Vladimir Stajic, Lesley Braun) for sponsoring the trial medications and consumables. We thank our food and beverage sponsors (Esther Leng Shu Wei, Prudential - The Advisors Group, WellSmoocht, CK, Delia.V, Doughin' Good, nomVnom, the Kind Bowl, and House on the Moon). This study is made possible through the close collaboration with the Tuas South Dormitory operations team (Than Lin Htaik, Mohd Amir Rahaman, Koh Shuwen), Tissue Repository Unit at the National University Hospital (Eng Chon Boon), NUH Research Office (Chng Wee Joo, Lee Meng Har), Deanery Office at the Yong Loo Lin School of Medicine (Chong Yap Seng, Lau Tang Ching, Aymeric Lim), Ministry of Health (Kenneth Mak, Tan Chorh Chuan, Derrick Heng), Health Sciences Authority (Lisa Tan) and Domain-Specific Review Board (Madelynn Chan Tsu-Li) and the multi-ministerial Joint Task Force (Dan Yock Young, Andrew Aw).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.04.035.

References

Abella BS, Jolkovsky EL, Biney BT, Uspal JE, Hyman MC, Frank I, et al. Efficacy and safety of hydroxychloroquine vs Placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. JAMA Intern Med 2020;181:195–202.

Anderson DE, Sivalingam V, Kang AEZ, Ananthanarayanan A, Arumugam H, Jenkins TM, et al. Povidone-iodine demonstrates rapid in vitro virucidal activity against SARS-CoV-2, the virus causing COVID-19 disease. Infect Dis Ther 2020;9:669–75.

Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020;383:517–25.

Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020;178:104787, doi:http://dx.doi.org/10.1016/j.antiviral.2020.

Chen JI, Yap JC, Hsu LY, Teo YY. COVID-19 and Singapore: from early response to circuit breaker. Ann Acad Med Singap 2020;49:561–72.

Dong L, Zhou J, Niu C, Wang Q, Pan Y, Sheng S, et al. Highly accurate and sensitive diagnostic detection of SARS-CoV-2 by digital PCR. Talanta 2021;224:121726.

Feyaerts AF, Luyten W. Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19?. Nutrition 2020;79–80:110948, doi:http://dx.doi.org/10.1016/j.nut.2020.110948.

Frank S, Brown SM, Capriotti JA, Westover JB, Pelletier JS, Tessema B. In vitro efficacy of a povidone-iodine nasal antiseptic for rapid inactivation of SARS-CoV-2. JAMA Otolaryngol Head Neck Surg 2020;146:1–5.

Goldman A, Bomze D, Dankner R, Hod H, Meirson T, Boursi B, et al. Cardiovascular adverse events associated with hydroxychloroquine and chloroquine: a comprehensive pharmacovigilance analysis of pre-COVID-19 reports. Br J Clin Pharmacol 2020;87:1432–42.

Hoffmann M, Mösbauer K, Hofmann-Winkler H, Kaul A, Kleine-Weber H, Krüger N, et al. Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. Nature 2020;585:588–90.

Hunter J, Arentz S, Goldenberg J, Yang G, Beardsley J, Mertz D, et al. Rapid review protocol: Zinc for the prevention or treatment of COVID-19 and other coronavirus-related respiratory tract infections. Integr Med Res 2020;9:100457, doi:http://dx.doi.org/10.1016/j.imr.2020.100457.

Koh D. Migrant workers and COVID-19. Occup Environ Med 2020;77:634–6.

Lee VJ, Chiew CJ, Khong WX. Interrupting transmission of COVID-19: lessons from containment efforts in Singapore. J Travel Med 2020;27:, doi:http://dx.doi.org/10.1093/jtm/taaa039 in press.

Li J, Thoon KC, Chong CY, Maiwald M, Kam KQ, Nadua K, et al. Comparative analysis of symptomatic and asymptomatic SARS-CoV-2 infection in children. Ann Acad Med Singap 2020;530–7.

Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020;6:16, doi:http://dx.doi.org/10.1038/s41421-020-0156-0.

Maisonnasse P, Guedj J, Contreras V, Behillil S, Solas C, Marlin R, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. Nature 2020;585:584–7.

Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet 2020;, doi:http://dx.doi.org/10.1016/S0140-6736(20)31180-6.

Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. N Engl J Med 2020;384:417–27.

Nikolai LA, Meyer CG, Kremsner PG, Velavan TP. Asymptomatic SARS Coronavirus 2 infection: invisible yet invincible. Int J Infect Dis 2020;100:112–6.

R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.

Rakedzon S, Neuberger A, Domb AJ, Petersiel N, Schwartz E. From hydroxychloroquine to ivermectin: what are the anti-viral properties of anti-parasitic drugs to combat SARS-CoV-2?. J Travel Med 2021;, doi:http://dx.doi.org/10.1093/jtm/taab005 in press.

Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323:2493–502.

Singapore Ministry of Health 2020. https://www.moh.gov.sg/covid-19 [Accessed 5 March 2021].

Stevenson A, Kirresh A, Conway S, White L, Ahmad M, Little C, et al. Hydroxychloroquine use in COVID-19: is the risk of cardiovascular toxicity justified?. Open Heart 2020;7:e001362, doi:http://dx.doi.org/10.1136/openhrt-2020-001362.

Sun Y, Koh V, Marimuthu K, Ng OT, Young B, Vasoo S, et al. Epidemiological and clinical predictors of COVID-19. Clin Infect Dis 2020;71:786–92.

Tan JB, Cook MJ, Logan P, Rozanova L, Wilder-Smith A. Singapore's pandemic preparedness: an overview of the first wave of COVID-19. Int J Environ Res Public Health 2020a;18:252, doi:http://dx.doi.org/10.3390/ijerph18010252.

Tan THY, Toh MPHS, Vasoo S, Lye DCB, Ang BSP, Leo YS, et al. Coronavirus disease 2019 (COVID-19): the Singapore Experience. A review of the first eight months. Ann Acad Med Singap 2020b;49:764–78.

te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6:e1001176, doi:http://dx.doi.org/10.1371/journal.ppat.1001176.

Ternovoi VA, Lutkovsky RY, Ponomareva EP, Gladysheva AV, Chub EV, Tupota NL, et al. Detection of SARS-CoV-2 RNA in nasopharyngeal swabs from COVID-19 patients and asymptomatic cases of infection by real-time and digital PCR. Klin Lab Diagn 2020;65:785–92.

Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324:782–93.

Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020;71:732–9.

Yi H, Ng ST, Farwin A, Pei Ting Low A, Chang CM, Lim J. Health equity considerations in COVID-19: geospatial network analysis of the COVID-19 outbreak in the migrant population in Singapore. J Travel Med 2020;, doi:http://dx.doi.org/10.1093/jtm/taaa159 in press.

Young BE, Ong SWX, Ng LFP, Anderson DE, Chia WN, Chia PY, et al. Viral dynamics and immune correlates of COVID-19 disease severity. Clin Infect Dis 2020;, doi:http://dx.doi.org/10.1093/cid/ciaa1280 in press.