MEDIA RELEASE

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LARGE-SCALE STUDY SHOWS ORAL HYDROXYCHLOROQUINE AND POVIDONE-IODINE THROAT SPRAY CAN REDUCE SPREAD OF COVID-19 IN HIGH TRANSMISSION SETTINGS

Preventive regimen shown to be effective in reducing COVID-19 transmission in a large-scale randomised controlled trial conducted among healthy migrant workers in Singapore

Singapore, 25 April 2021 - A team of clinician-scientists from the National University Hospital (NUH); NUS Yong Loo Lin School of Medicine (NUS Medicine); NUS Saw Swee Hock School of Public Health; National University Cancer Institute, Singapore; and National University Heart Centre, Singapore has found that oral hydroxychloroquine and povidone-iodine throat spray were effective in reducing the spread of COVID-19 infection in high transmission settings. The study findings were published in the *International Journal of Infectious Diseases*[1], following a randomised clinical trial conducted among 3,037 healthy migrant workers quarantined in a large multi-storey dormitory in Singapore.

Lead author of the interventional clinical study, Associate Professor Raymond Seet, Senior Consultant, Division of Neurology, Department of Medicine, NUH and Department of Medicine, NUS Medicine said: "The repurposing of existing drugs is an important global strategy against COVID-19. Until mass-vaccination is successfully implemented globally, non-pharmacological interventions such as masking and physical distancing are the only proven measures to mitigate transmission of COVID-19. Notwithstanding, the outbreak has been challenging to contain around the world, as new case clusters continued to emerge and even surge in certain regions. This is the first study to demonstrate the benefits of prophylactic, or preventive, 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 are existing drugs that are easily available and have known safety profiles. This can represent a viable preventive strategy for individuals living in a closed and high-exposure setting, especially in areas and countries where COVID-19 vaccination is not available or widespread."

Trial design and oversight

Beginning April 2020, Singapore witnessed a surge in COVID-19 cases following widespread outbreaks in residential dormitories of migrant workers. Efforts to isolate and quarantine infected workers were challenging given the high population density in the dormitories.

As part of efforts to contain transmission among residents, a randomised controlled trial was conducted among healthy migrant workers quarantined in at Tuas South Dormitory, 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 (preventive) regimen of

[1] https://www.ijidonline.com/article/S1201-9712(21)00345-3/pdf

either oral hydroxychloroquine (400mg once, followed by 200mg/day), oral ivermectin (12mg once), povidone-iodine throat spray (3 times/day, 270 µg/day), oral zinc (80mg/day)/vitamin C (500mg/day) combination, or oral vitamin C, 500mg/day. Vitamin C is used as a comparator medication as it was a widely-used remedy during the pandemic, despite a lack of preclinical evidence of efficacy against coronaviruses.

The primary outcome was laboratory evidence of SARS-CoV-2 infection as shown by either a positive serologic test for SARS-CoV-2 antibody on Day 42, or a positive PCR test for SARS-CoV-2 at any time between baseline and Day 42.

A total of 3,037 asymptomatic healthy men aged between 21 and 60 years (mean age 33), who provided written informed consent and were willing to adhere to the study protocol were recruited. Enrolment began on 18 May 2020 and a recruitment period of 14 days was set to include as many asymptomatic participants as possible. Participants were excluded if they had any symptoms of respiratory illnesses (fever, cough, runny nose, sore throat and/or shortness of breath), dysgeusia (a distortion of the sense of taste) or anosmia (complete loss of smell) in the past one month, had a previous diagnosis of COVID-19, or met other exclusion criteria.

The trial was first publicised 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, 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 prior to randomisation. Participants were asked to report their symptoms daily using FormSG. 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 reportedly arising from the use of hydroxychloroquine for COVID-19 treatment. A 12-lead electrocardiogram was performed in all participants randomised to receive hydroxychloroquine[2].

Blood samples were collected from all participants at randomisation and 42 days later; extracted sera were analysed for antibody response to SARS-CoV-2. Results of participants

[2] 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 >140mmHg, diastolic blood pressure >85mmHg and heart rate >100 per min.

who underwent nasopharyngeal swabs for SARS-CoV-2 were retrieved from medical records to ascertain status of SARS-CoV-2 infection.

Outcomes of the randomised trial

Primary outcomes reported laboratory confirmed COVID-19 infection was diagnosed in 1,681 of 3,037 (55.4%) men. The frequency of COVID-19 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%) as compared with vitamin C (433 out of 619 participants, 70%). There were no statistically differences observed between zinc/vitamin C (300 out of 634 participants, 47%) and ivermectin (398 out of 617 participants, 64%), compared with vitamin C. Compared with vitamin C, significant absolute risk reductions were observed for oral hydroxychloroquine (21%) and povidone-iodine throat spray (24%).

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).

In terms of 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. No pneumonia requiring hospitalization or death occurred. A total of 309 men had COVID-19 diagnosed by COVID-19 RNA detection from nasopharyngeal swabs. Consistently, men with greater medication adherence were significantly less likely to be infected.

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% (in terms of absolute risk reduction) compared with vitamin C. These findings support *in vitro* data that suggest potent virucidal effects of povidone-iodine against SARS-CoV-2 potentially capable of creating a relatively resistant environment within the oropharyngeal space. A reduction in viral load could also possibly reduce the exposure of aerosolised 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 highest medication adherence with fewer reporting side effects and medication discontinuation as compared with vitamin C arm, thereby supporting their tolerability and future applications.

A/Prof Seet noted: “Vulnerable settings where transmission can go unchecked have been clearly identified throughout the pandemic. Such settings include cruise ships, prisons, refugee camps and meat processing facilities, where there may be a pressing need for additional means to prevent spread. These existing drugs could be used to complement existing safety measures in settings where transmission is high while awaiting roll out of a vaccine. Further research could analyse the effects in other populations such as older people and women, and in those with immune compromise and other significant comorbidities, over more prolonged periods of time.”

This 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 Authorisation (CTA2000053) by the Health Sciences Authority, which oversees all clinical trials in Singapore.

Chinese Glossary

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Institutions in the NUHS Group include the National University Hospital, Ng Teng Fong General Hospital, Jurong Community Hospital and Alexandra Hospital; three National Specialty Centres - National University Cancer Institute, Singapore, National University Heart Centre, Singapore and National University Centre for Oral Health, Singapore; the National University Polyclinics; Jurong Medical Centre; and three NUS health sciences schools – NUS Yong Loo Lin School of Medicine (including the Alice Lee Centre for Nursing Studies), NUS Faculty of Dentistry and NUS Saw Swee Hock School of Public Health.

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