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.

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Editorial

COVID-19 chemoprevention

Despite the enormity of COVID-19 pandemic and the many hundreds of clinical trials evaluating putative therapeutics, there have been very few randomised controlled trials (RCTs) of COVID-19 pre-exposure prophylaxis. RCTs provide the strongest evidence in this setting (Collins et al., 2020). This is particularly important in the politicised and febrile arena of COVID-19 medicines where claims and counter claims abound, and good clinical science has suffered. In this edition of *IJID* Seet et al. report a detailed and well conducted open cluster randomised trial of five different pre-exposure interventions in male migrant workers quarantined in isolated dormitories in Singapore (Seet et al., 2021). Early in the pandemic Singapore experienced an outbreak of COVID 19 in migrant workers, so the health authorities quarantined the male workers in a cordon sanitaire comprising adjacent housing blocks with separated dormitories on each floor. Each floor could be isolated, and the migrant workers were prevented from intermixing with other floors. Infection prevention precautions were advocated and supported, individual meals were provided to reduce social mixing, and the quarantine was enforced with characteristic efficiency. This unusual circumstance provided an ideal opportunity to evaluate preventive interventions in a cluster randomised trial. Overall, there were 42 potentially evaluable clusters (dormitories). The interventions were vitamin C (500 mg once daily - the reference arm), zinc and vitamin C (40/250 mg twice daily), povidone-iodine throat spray (three times daily; equivalent to 8.1 mg iodine/month), and hydroxychloroquine (400 mg salt loading dose then 200 mg/day) all given for six weeks, and ivermectin (200 μg/kg) which was given only once. The study primary end point was a SARS-CoV2 infection diagnosed either by nasopharyngeal swab qPCR or by seroconversion. The six week trial enrolled 3037 men (mean age 33 years), most of whom were from India and Bangladesh. Unfortunately the hydroxychloroquine arm had strict cardiovascular exclusion criteria imposed because of safety concerns raised by the now retracted paper by Mehra et al. (one of many indirect scientific casualties of this fabricated research) (Mehra et al., 2020). As a result, this arm was significantly smaller than the other arms. The overall attack rate was high; 55.4% (1681 of 3037) of the men became infected, but none needed hospitalisation, and none died. In a logistic regression analysis, with adjustment for clustering, the attack rate in the hydroxychloroquine and the povidone-iodine throat spray groups was reduced compared with the Vitamin C only reference arm. The absolute risk reductions (98.75% confidence interval) were 21% (2–42%) in the men who received hydroxychloroquine (n = 432) and 24% (7–39%) in those who took the povidone-iodine throat spray (n = 735).

What do the results of this carefully conducted and relatively large study mean for the prevention of COVID-19? They are certainly not conclusive, as the number of clusters per treatment arm is small, and the hydroxychloroquine arm had the additional exclusion criteria which significantly reduced the number of eligible participants. The dynamics of infection within clusters can probably never be characterised sufficiently for adequate adjustment. But the results are indicative, and they make an important contribution to the small RCT evidence base on COVID-19 chemoprophylaxis. The positive results with the povidone-iodine throat spray (Guenezan et al., 2021; Burton et al., 2020) are intriguing and, although not conclusive, they certainly warrant further study given the simplicity and low cost of the spray. Zinc has had an enthusiastic and often vociferous minority following in COVID-19, but there is little evidence so far in its support (Thomas et al., 2021), and these results do not provide further encouragement.

Ivermectin is widely recommended for the treatment of COVID-19, particularly in South America, without good evidence of benefit (Mega, 2020). A small randomised comparison in 24 patients with acute COVID-19 showed a non-significant difference in viral clearance rates in favour of ivermectin, and several randomised comparisons have been posted before peer review, but there is really no convincing evidence reported to date (Chaccour et al., 2021; Ahmed et al., 2021). However, the negative result with ivermectin ($t_{1/2}\beta$ ~18 h) in the Singapore study should not be overinterpreted as only a single relatively low dose (12 mg) was administered, although there was no obvious difference in infection rates in the first week after administration. Clear evidence that ivermectin (or indeed any other putative antiviral) has a significant in-vivo antiviral effect in COVID-19 should be provided before embarking on any further investigation in prevention or treatment.

The lower incidence of COVID-19 infections in the hydroxychloroquine recipients in the Singapore cluster randomised trial (Seet et al., 2021) should be viewed in the context of current World Health Organization COVID-19 therapeutic guidelines and their negative recommendations (World Health Organization, 2021a, 2021b; Siemieniuk et al., 2020; Lamontagne et al., 2021). Hydroxychloroquine has had a torrid time in COVID-19. Like many of the

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potential repurposing candidates it has modest activity against SARS-CoV2 and several other viruses in experimental systems. Early claims of benefit in the treatment of hospitalised patients with hydroxychloroquine, based on uncontrolled observations, were followed by premature emergency use authorisations, intense politicisation, extreme views, and widespread unjustified use in treatment and potentially dangerous self-medication. Then, in May 2020, came the aforementioned highly publicised claim that hydroxychloroquine caused lethal ventricular arrhythmias in hospitalised patients (Mehra et al., 2020). The reaction from several regulatory authorities was immediate-stopping both use and study of hydroxychloroquine. *The Lancet* paper was subsequently shown to be fraudulent, and was retracted, but the damage was done. Recruitment to pre-(PrEP) and post exposure prophylaxis (PEP) trials plummeted, and a substantial negative perception about the safety of these drugs persists to this day.

From June 2020 findings from the largest randomised controlled trials, RECOVERY and SOLIDARITY began to emerge. These provided unequivocal evidence that hydroxychloroquine treatment was ineffective in hospitalised patients (as well as good news that dexamethasone was life-saving) (RECOVERY collaborative group et al., 2020, 2021; SOLIDARITY et al., 2021). Based largely on these inpatient studies (87.4% of patients studied in the RCTs were hospitalised), the WHO therapeutic guidelines in December 2020 recommended strongly against hydroxychloroquine treatment — but they extended this proscription to patients with any disease severity (World Health Organization, 2021a). There never was justification to recommend hydroxychloroquine for prevention or treatment outside randomised controlled trials. But the extrapolation of lack of efficacy of antiviral drugs in severe disease to uncomplicated infections was certainly not warranted by the available evidence (White et al., 2021). This is because COVID-19 illness reflects a changing pathological process. Viral burdens peak early, around the onset of first symptoms. This is the time when antiviral drugs are likely to be most beneficial. Thereafter viral burdens decline and inflammatory processes dominate in those patients who deteriorate and require hospitalisation, and ultimately respiratory support. In March 2021 WHO, extended their guidelines to chemoprevention. The Guidelines group strongly recommended against hydroxychloroquine in chemoprophylaxis. They further suggested that ongoing research should be "reconsidered" (i.e. discontinued). This strong recommendation was because they had concluded that there was "high certainty evidence" that hydroxychloroquine was ineffective in preventing COVID-19, and that there was "moderate certainty evidence" that adverse events leading to drug discontinuation were a significant problem for hydroxychloroquine prophylaxis (Siemieniuk et al., 2020; World Health Organization, 2021b). Yet, before the Singapore trial, there had been only three published RCTs evaluating hydroxychloroquine in post-exposure prophylaxis, and only two in pre-exposure prophylaxis (another has been posted as a preprint) (Abella et al., 2021; Grau-Pujol et al., 2020; Rajasingham et al., 2020). These six randomised controlled comparisons combined together enrolled 6059 participants, but they employed varied methodologies, different dose regimens, and they generated few endpoints. There were only 26 confirmed COVID-19 cases in total (15 out of 1197 randomised to hydroxychloroquine, 11 out of 687 randomised to placebo) in the three PrEP trials (Schilling et al., 2021). This compares with 645 COVID-19 cases in the hydroxychloroquine and reference comparator (Vitamin C) groups in the Singapore study (Seet et al., 2021). Nevertheless, despite the tiny number of endpoints in the studies they reviewed, the WHO guidelines group were somehow able to conclude with "high certainty" in their GRADE assessment (Guyatt et al., 2008) that hydroxychloroquine provided no useful benefit (Siemieniuk et al., 2020; World Health Organization, 2021b). In addition, their adverse events assessment contains a mistake (miscoding of one of the study results) (Siemieniuk et al., 2020; World Health Organization, 2021b). After correction of this mistake the rate of discontinuations in hydroxychloroquine recipients is not significantly different to those receiving placebo (Schilling et al., 2021). This good tolerability and adherence is supported by the Singapore study. A meta-analysis of the six heterogeneous trials evaluated by the WHO guidelines, using the trial pre-specified end-points, is in the direction of protective benefit from hydroxychloroquine (García-Albéniz et al., 2021), as is the result of the current study. Seet et al. conclude correctly that the question remains open. There is certainly not enough evidence to support the WHO guidelines claim of high certainty evidence for lack of useful benefit (Schilling et al., 2021).

The WHO guidelines surmised that "*Mortality would be the outcome most important to individuals, followed by need for hospital admission, laboratory confirmed SARS-CoV-2 infection, and adverse effects leading to discontinuation*" (Siemieniuk et al., 2020; World Health Organization, 2021b). They determined that there were no important differences in mortality in the RCTs. But there were only 13 deaths in total in the six prophylaxis trials, all from one cluster-randomised, non-blinded, post-exposure prophylaxis (PEP) trial (Mitjà et al., 2021). So, without a single death in the three pre-exposure prophylaxis (PrEP) RCTs reviewed, and a highly unstable odds ratio of 0.67 for mortality in subjects allocated to hydroxychloroquine versus those who did not in the PEP RCTs (95% C.I. 0.22–2.05), the panel concluded somehow that this provided "*high certainty evidence*" that hydroxychloroquine pre-exposure prophylaxis does not reduce COVID-19 mortality (Siemieniuk et al., 2020; World Health Organization, 2021b). For the WHO's "*second most important outcome*" in the six RCTs, there were only 49 hospital admissions in total (20 in the PrEP RCTs; 11 hydroxychloroquine, 9 placebo). In the PrEP studies only 2 admissions were for COVID-19. There were no deaths and no hospital admissions in the Singapore study, so no further light can be cast on the strange conclusions of the WHO Guidelines.

The Singapore study reported by Seet et al. provides valuable information on safety, tolerability and efficacy of potential chemoprevention interventions. It confirms that chemoprophylaxis is generally acceptable. For hydroxychloroquine it emphasizes that there remains uncertainty whether or not hydroxychloroquine prophylaxis provides a modest but potentially useful protection against COVID19 infection, and that at "rheumatoid arthritis" doses, it is well tolerated. It has not been easy to conduct chemoprevention studies in COVID-19, and many trials have failed to reach their planned targets. This trial is an important achievement. Overall, in contrast to the high protective efficacy of vaccines, no definitive conclusions can be drawn from the studies to date of small molecule drugs in chemoprevention, which have been powered only to identify large effects. However, sustained high vaccine efficacy cannot be guaranteed as SARS-CoV2 continues to evolve and vaccine deployment globally is slow. There is still a need to identify medicines which can protect against COVID-19.

Note

The authors are investigators on the COPCOV study; chloroquine/hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study.

Conflict of interest

No conflict of interest to declare.

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Ethical approval

Approval was not required.

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