Sir,

We read with interest the paper by Zhou et al. proposing the use of hydroxychloroquine (HCQ) for therapeutic and prophylactic purposes against SARS-CoV-2 infection. Zhou et al. pointed out that HCQ is effective in inhibiting the entry of the virus into host cells. Zhou et al. also highlighted that HCQ is immunomodulatory and inhibits the Th1 response, thus preventing a cytokine storm from happening in COVID-19 patients. They concluded that HCQ is an attractive candidate for therapeutic and prophylactic use given its antiviral activity, immunomodulatory function and excellent safety record. We here contend that, although HCQ may be useful as a therapeutic agent, caution should be exercised in using HCQ as a prophylactic agent.

The use of HCQ as a prophylactic agent may increase the initial viral load, should prophylaxis fail and infection occur, due to the suppression of the Th1 response by HCQ. The result from a randomized trial on the effect of HCQ in decreasing immune activation by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1alpha) and IL-6 in human monocytes and T cells. Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1alpha) and IL-6 in human monocytes and T cells. J Rheumatol 1993; 20: 803–8.

use of HCQ as a prophylactic agent against SARS-CoV-2 infection. Although the common side effects of HCQ at a prophylactic dose against malaria, such as pruritus, headache and gastrointestinal upset, are generally mild, HCQ interacts with many commonly used medicines and may lead to serious side effects. HCQ was reported to increase the risk of neuropsychiatric adverse events when used with the antivirals indinavir, nelfinavir and ritonavir (one of the proposed medicines against SARS-CoV-2 infection) or aminoglycoside antibiotics at doses used for treating rheumatic diseases. Interaction between HCQ and a QT-prolonging agent or a QT-shortening agent (digoxin) also increases the risk of arrhythmias. In addition, with long plasma half-lives (1300 h for HCQ and 900 h for chloroquine (CQ)), HCQ and CQ may accumulate in the body and be passed to babies via breast milk, although no permanent harm has been reported so far in humans. With all these concerns, the safe and effective prophylactic dosage and the eligibility criteria would be the critical parameters to be determined and considered in the decision-making process of adopting HCQ for prophylaxis. It was suggested that doses below 6.5 mg/kg/day for HCQ and 3 mg/kg/day for CQ are well tolerated by patients in general. A double-blinded, randomized clinical trial of CQ was launched recently to investigate the protective effect of CQ in a healthcare setting against COVID-19 infection. A similar study should be conducted to determine the protective effect of HCQ.

Given that a vaccine against SARS-CoV-2 has yet to be developed, prescribing HCQ for prophylaxis may be a favourable option for protecting the healthy population from infection, slowing the pandemic and reducing the pressure put on the healthcare system. However, given the risks of worsening prognosis and the possible adverse effects on certain population groups, caution should be exercised in using HCQ for prophylaxis. Further research through clinical trials is required to identify: (i) the effect of HCQ on initial viral load; (ii) the individuals who may benefit or may be harmed; and (iii) the optimal dose and duration. The information obtained will help in the design of a prophylactic regimen with adequate protection without compromising the immune system.

Transparency declarations
None to declare.

References
1 Zhou D, Dai S-M, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother 2020; doi:10.1093/jac/dkaa114.
2 Paton NI, Goodall RL, Dunn DT et al. Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: a randomized controlled trial. JAMA 2012; 308: 353–61.
3 Sperber K, Quraishi H, Kalb TH et al. Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human monocytes and T cells. J Rheumatol 1993; 20: 803–8.
Fox RI, Kang HI. Mechanism of action of antimalarial drugs: inhibition of antigen processing and presentation. Lupus 1993; 2 Suppl 1: S9–12.

Chu CM, Poon LL, Cheng VC et al. Initial viral load and the outcomes of SARS. CMAJ 2004; 171: 1349–52.

Stokkermans TJ, Trichonas G. Chloroquine and Hydroxychloroquine Toxicity. StatPearls Publishing, 2019.

Haladyj E, Sikora M, Felis-Giemza A et al. Antimalarials—are they effective and safe in rheumatic diseases? Rheumatologia 2018; 56: 164–73.

Health Service Executive. Specific Antiviral Therapy in the Clinical Management of Acute Respiratory Infection with SARS-CoV-2 (COVID-19). 2020.

Rosa SGV, Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. Pan Am J Public Health 2020; 44: e40.