

authors enrolled 821 participants, an illness that was confirmed by polymerase-chain-reaction assay in less than 3% of the participants. The incidence developed in 107 participants (13.0%) but was expected to be consistent with Covid-19 participants who were asymptomatic (16.8%). No serious reactions were reported.

This trial has many limitations, acknowledged by the investigators. The trial methods did not allow consistent laboratory confirmation of SARS-CoV-2 or participant-reported symptoms is low⁶, so it is hard to be certain how many participants in the trial actually had symptoms. In addition, those receiving hydroxychloroquine, more notably in the group that adhered perfectly to the trial, were more likely to develop severe Covid-19 than persons in whom severe Covid-19 is most likely to develop⁷, so enrollment of higher-risk participants might have yielded a different result.

The trial design raises questions about the expected prevention benefits of hydroxychloroquine. The trial design did not ask questions about the postexposure prophylaxis arm. Studies of postexposure prophylaxis are

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), has generated a worldwide pandemic. The interruption of its spread depends on a combination of pharmaceutical and nonpharmaceutical interventions. Initial SARS-CoV-2 prevention includes social distancing, the use of face masks, environmental hygiene, and hand washing.¹ Although the most important purpose of established drugs for short-term prevention of illness from a variety of microorganisms, including SARS-CoV-2, hydroxychloroquine can inhibit replication of SARS-CoV-2 in vitro.² Some observational studies have suggested benefits of hydroxychloroquine for the treatment of Covid-19, whereas other treatment regimens of Covid-19, such as postexplosive prophylaxis for chloroquine as a randomized trial testing hydroxychloroquine or a pragmatic trial recruiting participants with Covid-19,³ this is described by the investigators as a "pragmatic" trial in which participants were recruited through social media and almost all who described a high-risk or moderate-risk exposure to someone with Covid-19 in their house-hold or an occupant setting were provided 4 days after the reported exposure, and before hydroxychloroquine or placebo (by mail) within 4 days of symptom onset. Adults were reported by the participants to be mostly 40 years old or younger, and the mean age was 35 years. The study included 1000 participants, and the primary outcome was the rate of hospitalization or death at 28 days. The results showed that hydroxychloroquine was associated with a lower rate of hospitalization or death compared with placebo (11.6% vs 16.1%, adjusted hazard ratio 0.68, 95% confidence interval 0.48-0.88).⁴ The authors concluded that hydroxychloroquine may reduce the risk of hospitalization or death in patients with Covid-19, but the evidence is limited by the study design and the lack of a placebo-controlled trial. The results of this study should be interpreted with caution, as the study was not placebo controlled and the sample size was relatively small.

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Hydroxychloroquine for the Prevention of Covid-19 — Searching for Evidence



EDITORIALS

intended to provide an intervention in the shortest possible time to prevent infection. In a small-animal model of SARS-CoV-2 infection,⁸ prevention of infection or more severe disease was observed only when the experimental antiviral agent was given before or shortly after exposure. In the current trial, the long delay between perceived exposure to SARS-CoV-2 and the initiation of hydroxychloroquine (≥ 3 days in most participants) suggests that what was being assessed was prevention of symptoms or progression of Covid-19, rather than prevention of SARS-CoV-2 infection.

Drugs for the prevention of infections must have an excellent safety profile. When hydroxychloroquine was initially promoted as a possible solution to SARS-CoV-2 infection, the safety of the drug was emphasized.² Under closer scrutiny, however, the potential for cardiac toxic effects and overall adverse outcomes have been emphasized, especially in persons with underlying co-existing conditions that increase the risk of severe Covid-19.⁹ Boulware et al. report frequent mild side effects of hydroxychloroquine, but cardiac toxic effects could not be assessed.

So, what are we to do with the results of this trial? The advocacy and widespread use of hydroxychloroquine seem to reflect a reasonable fear of SARS-CoV-2 infection. However, it would appear that to some extent the media and social forces — rather than medical evidence — are driving clinical decisions and the global Covid-19 research agenda.¹⁰ On June 1, 2020, ClinicalTrials.gov listed a remarkable 203 Covid-19 trials with hydroxychloroquine, 60 of which were focused on prophylaxis. An important question is to what extent the article by Boulware et al. should affect planned or ongoing hydroxychloroquine trials. If postexposure prophylaxis with hydroxychloroquine does not prevent symptomatic SARS-CoV-2 infection (with recognition of the limitations of the trial under discussion), should other trials of postexposure prophylaxis with hydroxychloroquine continue unchanged? Do the participants in these trials need to be informed of these results? Do these trial results with respect to postexposure prophylaxis affect trials of

preexposure prophylaxis with hydroxychloroquine, some of which are very large (e.g., the Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine [HERO-HCQ] trial, involving 15,000 health care workers; ClinicalTrials.gov number, NCT04334148)? The results reported by Boulware et al. are more provocative than definitive, suggesting that the potential prevention benefits of hydroxychloroquine remain to be determined.

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