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.

assessment for G6PD deficiency before initiating hydroxychloroquine treatment.[2] In the largest US study[2] to evaluate the frequency of G6PD deficiency in patients taking hydroxychloroquine, there were no reported episodes of haemolysis in more than 700 months of hydroxychloroquine exposure among the 11 G6PD-deficient patients. Even though similar studies of chloroquine are not available, there are no reports of haemolysis associated with chloroquine monotherapy either.[3]

In the same context, since conduction abnormalities and cardiomyopathy (from long-term use of hydroxychloroquine) are quite rare adverse events, no guidelines recommend that a routine cardiac evaluation be done before initiating hydroxychloroquine treatment.[4] We acknowledge that the Mayo clinic has recommended baseline electrocardiogram monitoring of patients with COVID-19 before starting hydroxychloroquine treatment.[5] However, this recommendation appears to be specific to COVID-19, since the disease per se can have clinically significant cardiopulmonary involvement.[6]

To conclude, although there is renewed global interest in hydroxychloroquine at present, only time will tell how beneficial the recommendations regarding the global use of this drug during the COVID-19 pandemic will be, given that evidence of its effectiveness in this setting is scarce. However, if this drug is found to be beneficial, the fear of haemolysis should not deter one from the prescription of hydroxychloroquine.

We declare no competing interests.

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Making decisions to mitigate COVID-19 with limited knowledge

On March 11, 2020, WHO declared the coronavirus disease 2019 (COVID-19) outbreak a global pandemic. Aggressive actions should be taken immediately to mitigate the spread of severe acute respiratory syndrome coronavirus 2. In their Comment, Yonghong Xiao and Mili Estee Torok[1] rightly stated that infection prevention and control measures should be based on sound scientific principles. However, we disagree with the authors' views on certain measures that they consider to have "no scientific basis and have proven to be ineffective". A difference exists between measures with unknown effectiveness and those that have been proven ineffective or of no value.

We disagree with Xiao and Torok's view that "the practice of blocking traffic and lockdown of villages is of no value for the prevention and control of COVID-19". One of the references provided to support this statement was a local transport authority policy reported in a newspaper, which should not be considered as scientific evidence. Several studies have been done to assess the effectiveness of travel restrictions,[2,3] and the benefit of such restrictions might vary in different settings. Further studies and more data are required to reach a solid conclusion.

With regard to hospital treatment of patients with COVID-19, Xiao and Torok suggested that patients should not be given drugs of unknown efficacy. However, considering that no treatments are known to be effective at present, we believe that off-label or compassionate use of drugs should be considered ethical, especially for patients with life-threatening infections. However, when considering off-label or compassionate use of drugs, the safety profile of the drug should be clear and the clinicians should carefully balance the risk and potential benefit of use—an approach used in the first report of remdesivir use for the treatment of COVID-19.[4]

During this urgent phase of the COVID-19 pandemic, decisions at the level of the public health response or clinical management have to be made using the scarce data available. Scientific evidence will be gradually established as a result of ongoing research. However, measures that have good rationale, but for which little data are available (eg, travel restrictions, lockdowns, and compassionate use of drugs), should also be considered as options and should be assessed and amended in a continuous manner.

We declare no competing interests.

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Published **Online** April 7, 2020 https://doi.org/10.1016/S1473-3099(20)30280-2

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Plea for multitargeted interventions for severe COVID-19

Severe coronavirus disease 2019 (COVID-19) is not just a serious respiratory viral disease, as influenza is, but rather a systemic multiorgan viral invasion. It is frequently complicated by overwhelming immunological reactions, with overactivation of T cells, leading to acute respiratory distress syndrome and multiorgan failure, secondary to immunopathological processes. The viral load of severe acute respiratory syndrome coronavirus 2 is not correlated with worsening symptoms, but it is the host inflammatory response that is a major cause of lung damage and subsequent mortality.[1,2] Hyper-inflammatory responses in patients with COVID-19 are associated with a cytokine storm that is characterised by an increase in proinflammatory cytokines, including tumour necrosis factor, interleukin (IL)-1β, IL-6, and other chemokines in serum.[3,4] Overwhelming secretion of cytokines causes severe lung damage, which manifests as extensive damage to pulmonary vascular endothelial cells and alveolar epithelial cells, as well as increased pulmonary vascular permeability, leading to pulmonary oedema and hyaline membrane formation.[2–4]

Most clinical trials to date have evaluated various strategies of antivirals, immunomodulators, host-targeted drugs, immune-based therapies, or immunosuppressive drugs, including steroids, IL-6 or IL-1 antagonists, and selinexor; all have assessed single drugs with a clinical endpoint using the WHO seven-point ordinal scale.[5] Although some of these drugs might have clinically meaningful effects on viral burden or some of the immune-related signs, it is highly improbable that a single drug will be enough to control and improve the most severe forms of COVID-19. It is likely that both antivirals and blockage of inflammatory pathways are needed to optimise responses. For example, it would be relevant to understand the role of steroids in combination with or sequential to antiviral treatments. Without studying combinations, and their potential synergies or additive effects, potentially useful agents could be disregarded. Furthermore, in the absence of synergistic combinations, single drugs might cause more harm—for example, mass killing of the virus might enhance inflammatory responses. Because of the urgency of the current situation and, so far, an absence of clear evidence of a clinically meaningful effect of any monotherapy strategy, investigators should join their efforts in proposing, rather than adaptive or sequential studies of a single strategy, combined approaches through multifactorial designs. This approach will enable determination of the risks and benefits of combinations versus monotherapies. Such trials with multifactorial designs (eg, with randomisation first to antivirals and then to adjunctive immune-based therapy) are urgently needed and could provide more rapidly clinically meaningful results.

Furthermore, with improving knowledge of the various clinical presentations of COVID-19, better definitions of patient populations at highest risk of poor outcomes, based not only on clinical status but also on biomarkers (eg, C-reactive protein, D-dimer, ferritin, and IL-6), should be incorporated into inclusion criteria and stratifications.[6] Finally, the optimal timing or sequence of administration of the components of therapy during a worsening COVID-19 disease course need to be explored. We call for collaboration between pharmaceutical companies, institutions, and policy makers to either allow individuals to be enrolled simultaneously in trials of different investigational drugs with distinct targets or to collaborate on trials that include study arms that investigate combination therapy.

J-FB reports personal fees from AbbVie, AstraZeneca, Bayer, BMS, Gilead, GSK, Lilly, Novartis, Pierre Fabre, Roche, Sanofi, Takeda, and ViiV Healthcare, outside this work. JRA reports being an investigator on clinical trials for Gilead, Roche, and Xanofi, outside this work. SW reports grants, personal fees, non-financial support, and other from Merck, Gilead, ViiV Healthcare, GSK, and Janssen, outside this work. FR reports personal fees from Gilead, Janssen, MSD, Theratechnologies, and ViiV Healthcare, outside this work. All other authors declare no competing interests.

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