The recent publication of Pradelle et al., who estimated almost 17,000 deaths related to hydroxychloroquine use in COVID-19 patients has received a lot of attention from the media and is causing political turmoil. In an interview consequent to the publication of that article, the last author also lauched precise accusations to people who hoped that hydroxychloroquine might exert some benefit in COVID-19 patients and authorized its emergency use [https://www.rts.ch/info/sciences-tech/medecine/14600768-jean-christophe-lega-il-aurait-fallu-inclure-l-hydroxychloroquine-dans-un-essai-avant-de-la-recommander.html?rts_source=rss_t].

 # Our reply

That's not related to the article and that's not what is written or said in the link provided. The communication regarding this publication has not been commented on by the employers of the last author (Hospices Civils de Lyon and Université Lyon 1) or the Conseil National de l'Ordre des Médecins (i.e. the Medical Council ensuring compliance with medical ethics in France). We specifically highlighted the challenges faced by physicians during the first wave due to the lack of data and the pressure from patients to receive treatments (1).

Following the digital harassment, we have experienced, including false accusations and defamation, the Lyon 1 University has provided legal assistance for the defense of the last author (Jean-Christophe Lega).

You may understand the consequences of this turmoil. I respect the choice of the journal supporting an unorthodox point of view because its methods were described in detail, thus allowing replication or falsification.

 # Our reply

It is unclear why the point of view in our article is assessed as 'unorthodox'. It is unclear what that means "allowing falsification".

The open-mindedness of the journal should therefore be shown also with the publication of a falsification of the data presented by Pradelle et al., in order to allow scientific debate to be opened and let the scientific community reach conclusions that be largely agreed upon.

 # Our reply

It is unclear what would be "a falsification of the data".

Although we were initially supportive of chloroquine/hydroxychloroquine repurposing during the SARS-CoV-1 epidemic [1], also due to initially promising in-vitro data [2,3], we noticed throughout the years that the drug dosages administered in clinical trials for treatment of different viral diseases could hardly result in tissue drug levels able to carry out any significant antiviral effect [4,5]. In a retrospective analysis of the clinical trials aimed at limiting residual viral replication and the related immune hyperactivation in people living with HIV/AIDS, which were conducted before the pandemic, we noticed that the bulk of the clinical data indicated that chloroquine/hydroxychloroquine was unlikely to exert a marked beneficial effect on HIV-related immune activation [6]. Using a mathematical model, we showed, during the first wave of the pandemic, that, at the recommended dosages, hydroxychloroquine was unlikely to exert significant effects on SARS-CoV-2 replication in the pharynx in the absence of an effective

immunity [7]. Accordingly, the results of clinical trials of hydroxychloroquine as an antiviral agent for COVID-19 have been mixed or disappointing [8]. Instead, from a drug safety perspective, the drug appeared to be moderately tolerated in diverse populations [9-11] with non-significant differences in mortality between hydroxychloroquine vs. standard-of-care treated patients [8], despite an initial alarmist report that was later retracted [12]. Strict monitoring of the Q/T prolongation revealed very helpful in limiting the cardiac side effects in hydroxychloroquine-treated patients [13,14].

 # Our reply

That is not related to the article. We are very surprised by reference [8], as it does not correspond to a meta-analysis dedicated to assessing drug effects. The author's opinion appears well measured regarding the use of a molecule increasing the risk of death (2) or mechanical ventilation (3).

Therefore, it was rather surprising to read the report of Pradelle et al. [15], which estimates 16,990 excess deaths related to hydroxychloroquine use in COVID-19 patients in six countries including Italy. The details of their published analysis indicate that the authors used the following formula: N of deaths = (N hospitalized patients) x (mortality rate) x (HCQ exposure) x (OR HCQ related death) wherein HCQ is hydroxychloroquine and the odds ratio (OR) of 1.11 was applied to the calculations, as derived from a metaanalysis largely dominated by the RECOVERY and WHO SOLIDARITY trials [16]. In those trials, hydroxychloroquine was administered starting from an extremely high loading dose (i.e. 2400 mg/24 h) [17,18], which overlaps with an overtly toxic dosage [19].

 # Our reply

The doses used in the trials are based on PK/PD modeling, allowing for the achievement of therapeutic concentrations (4,5). The reference [19] does not question the doses used in the trials.

This risky choice was done to overcome the aforementioned limitations of the dosages till then adopted in clinical trials of hydroxychloroquine as an antiviral agent. As a consequence, toxic side effects may have occurred that might have overshadowed the potential benefits in terms of antiviral activity. Fortunately, the RECOVERY trial dosage was not adopted on a large scale. For example, the Italian Infectious Disease Society (SIMIT) recommended, during the first wave of the pandemic, a hydroxychloroquine dosage of 400 mg/day [20]. The regimen temporarily approved by the FDA for emergency use applied the same dosage, adding a loading dose of 800 mg in the first day of treatment [21]. This protocol was based on a published mathematical model [22]. In France, another country considered in the estimates of Pradelle et al. the posology of 400 mg/day was recommended by the national guidelines [23], while a dosage of 600 mg/day hydroxychloroquine (administered without a loading dose) was adopted in some clinical centers [24].

#Our reply

In France, the pharmacovigilance network has reported 8 deaths and serious adverse events during one month in COVID-19 patients despite national guidance (6). Consequently, it cannot be concluded that lower doses are free of lethal and non-lethal serious adverse effects, which is the argument put forth by the author of this letter.

In any case the dosage was significantly lower than that adopted in the RECOVERY and WHO SOLIDARITY trials.

Therefore, the hydroxychloroquine dosage from which the mortality OR was extrapolated by Pradelle et al. is not representative of the dosages administered in the real world.

 # Our reply
The author provides no references to support this argument based on real-world data. Conversely, we found a protocol using a loading dose of 1200 mg in frail patients during the first wave of COVID-19 (7).

Notwithstanding the apparent drug efficacy limitations described above, the estimates by Pradelle et al. on excess mortality should therefore be regarded with extreme caution.
#Our reply
In our study, we clearly highlighted the limitations in the precision of the estimation of HCQ's effect by meta-analysis of Axfors et al. (2). This meta-analysis was based on an updated database of the worldwide available evidence of the treatment effect of hydroxychloroquine on mortality for COVID-19. It relied on randomized trials, enabling a relative estimate of the treatment effect with a lower risk of bias compared to non-randomized studies.
We disagree with the arguments of Dr. Andrea Savarino, who presents a discussion that are poorly supported by evidence.

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