



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

## Journal of Infection and Public Health

journal homepage: <http://www.elsevier.com/locate/jiph>

Original Article

Hydroxychloroquine as antiviral prophylaxis for exposed caregivers to Covid-19: An urgent appraisal is needed<sup>☆</sup>Rachid Tahiri Joutei Hassani<sup>a,\*</sup>, Ahmed Bennis<sup>b</sup><sup>a</sup> Ambulatory Surgery Department, Avranches Granville Hospital, Granville, France<sup>b</sup> Cardiology Department, Jerada Clinic, Casablanca, Morocco

## ARTICLE INFO

## Article history:

Received 28 March 2020

Received in revised form 22 April 2020

Accepted 6 May 2020

## Keywords:

Coronavirus

Healthcare workers

Chloroquine

Antiviral prophylaxis

## ABSTRACT

**Background:** Since the onset of the new coronavirus pandemic, the world is facing a public health emergency. Repositioning hydroxychloroquine (HQ) seems to be a promising option. Many emerging evidences have converged on the effectiveness of HQ in the treatment of Covid-19 infection. In a recent paper, Gautret et al. suggested that further works are needed to determine if HQ antiviral prophylaxis is useful, especially for healthcare workers.

**Methods:** The purpose of this paper is to assess the Covid-19 exposure and risks level among caregivers. For this, we performed research on internet and PubMed by crossing the following keywords: healthcare givers, healthcare workers, doctors, nurses, coronavirus, Covid-19, mortality, infection rate, chloroquine, hydroxychloroquine.

**Results:** Data on healthcare worker's infection and mortality by Covid-19 are partial and are not systematically published. However, it seems that the infection rate varies between 3.8% and 9% depending on the country. Moreover, the mean age of this population is relatively old, especially in the OECD area.

**Conclusions:** Anti-Covid-19 HQ prophylaxis should be urgently assessed, especially for healthcare workers. It is to be hoped that HQ prophylaxis reduces the morbidity and mortality from Covid-19 infection among this population which is particularly exposed and relatively old.

© 2020 Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Hydroxy-chloroquine (HQ) is a cheap, safe and well-known drug that has been used for more than 70 years [1,2]. It is widely used as anti-malarial agent and has established immunomodulatory and anti-inflammatory activity; it has also proven clinical efficacy against a large variety of viral infections by increasing endosomal pH required for virus replication [2]. Considering the public health emergency since the onset of the new coronavirus pandemic, repositioning of this molecule is an interesting strategy because pharmacokinetics, safety profile, posology and drug interactions of HQ are well known [3–5]. Many emerging evidences have converged on the efficacy of HQ in the treatment of Covid-19 infection [3–9]. Multicenter clinical trials conducted in China showed apparent efficacy and acceptable safety against COVID-19

associated pneumonia [8]. In a recent series reported by Gautret et al. [9], the authors demonstrated that HQ treatment has a significant effect, both in terms of clinical outcome and viral clearance. At day 6 post-inclusion, 70% of hydroxychloroquine-treated patients were virologically cured comparing with 12.5% in the control group. Gautret et al. suggested that further works are needed to determine if HQ antiviral prophylaxis is useful, especially for healthcare workers [9].

We absolutely agree with this suggestion and believe that the HQ antiviral prophylaxis for healthcare workers should be considered and urgently assessed. Indeed, caregivers are in the frontline against the Covid-19 all around the world and are particularly exposed to Covid-19 infection. According to many reports, Thousands of nurses and doctors contracted the virus since the onset of the new coronavirus [10–14]. In China, among the 44,672 cases, a total of 1716 were healthcare workers (3.8%), as of February 11, 2020 [10]. In Italy, as of March 20th, 2020, according to the country's National Health Institute, seventeen doctors have died from Covid-19 and there are at least 3654 healthcare workers that have been infected, representing 9% of total cases [11–13]. In Paris, France, as of March 20th, 2020, there were 345 healthcare workers infected

<sup>☆</sup> Comment on: Gautret et al. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – doi:10.1016/j.ijantimicag.2020.105949.

\* Corresponding author at: Ambulatory Surgery Department, Avranches Granville Hospital, 849, Rue des Menneries, 50400 Granville, France.

E-mail address: [granville-tahiri@levisiologiste.com](mailto:granville-tahiri@levisiologiste.com) (R. Tahiri Joutei Hassani).

by the Covid-19 [14]. And as of March 23rd, 2020, five doctors have died from Covid-19 in France [15,16]. The number of infected healthcare workers is probably underestimated because they are not always tested [11].

Moreover, medical demography is increasingly aging in the OECD area (organization for economic cooperation and development area), 38% of doctors are over 55 [17]. In France, the mean age of doctors is 57 years and 41% of them over 60 [18]. Knowing that the morbidity and mortality rate from Covid-19 infection increases with age [10], it is to be feared that the human toll may be heavy among caregivers. As of March 23rd, 2020, the 5 died doctors in France were 60, 66, 67, 68 and 70 years old [15,16].

The high rate of infections among healthcare staff is a serious concern because healthcare workers who are infected must stay away from work for at least 14 days, depleting the already exhausted workforce [11,13,19,20]. In Iran, because of the lack of healthcare staff and the enormous number of patients, some nurses are forced to work 19h per day [20], and this situation could be worsened if some of the remaining caregivers contract the infection. The more healthcare staff is infected, the weaker the responsiveness of the healthcare system, particularly in a context of a chronic shortage of staff and means [19,20]. This vicious circle could increase mortality among Covid-19 hospitalized patients. It is important to preserve the healthcare reserve which is the back spine in the fight against Covid-19. This need is even more pressing in the developing countries where the medical demography is weaker, where the personal protection means as surgical and ffp2 masks are not sufficiently available and where any loss of this qualified workforce could have disastrous public health consequences.

Chemoprophylaxis is an established approach to potentially control infectious diseases and should be considered in the fight against COVID-19 pandemic [21]. Development of new vaccines and antivirals is time-consuming and expensive while the repositioning of available drugs should receive priority attention [21]. HQ has a long safety record, is inexpensive and widely available [2]. Considering that this drug is commonly prescribed in malaria prophylaxis when traveling to endemic malaria areas, and that this treatment can be prescribed for periods of up to several years [21], it would be logical to prescribe this molecule as prophylaxis for healthcare workers who are exposed to Covid-19, almost like when it is prescribed as prophylaxis for travelers to a malaria-endemic area. Moreover, antiviral prophylaxis would provide some psychological reinsurance that could reduce stress among caregivers who are at the forefront of the fight against Covid-19. It has been established that stress is a factor that can contribute to the physical and mental overwork and increase immune dysregulation [22], which would make caregivers even more susceptible to infection.

Recently, India has adopted an anti-viral prophylaxis protocol based on hydroxychloroquine for health professionals [23]. These recommendations are empiric and are not based on the results of a clinical trial. As of April 15th, 2020, Paris hospitals in France have begun a randomized trial in 900 participants, called PrEP Covid, to access both of HQ and azithromycin in Covid-19 prophylaxis, the trial will access a 200 mg per day posology of HQ, results are expected within 2–3 months [24].

Chang and Sun recommended safe and potentially efficacious dose regimens for protection against COVID-19 based on a review of chloroquine's antiviral mechanisms, its laboratory efficacy activity against COVID-19, as well as its pharmacokinetics in established indications. The authors recommended pre-exposure prophylaxis of 250–500 mg daily and post-exposure prophylaxis at 8 mg/kg/day for 3 days [21].

An urgent clinical assessment is needed to access the effectiveness of HQ anti Covid-19 chemoprophylaxis, the optimal dosage and the balance between the benefits and risks. Regarding the potential benefits: does anti-viral prophylaxis reduce the risk of

infection with Covid-19? In the event of infection, does it reduce the viral carriage and therefore the virus transmissibility? Does it reduce the percentage of serious forms requiring respiratory assistance? And does it reduce mortality among caregivers?

The antiviral prophylaxis study will also need to assess the tolerance profile and side effects of HQ. Regarding this point, there is already evidence of the rarity of serious events after treatment with antimalarial drugs [25,26]. Side effects are infrequent, mild and usually reversible. They include nausea, anorexia, abdominal pain, vomiting, dizziness, headache, blurry vision, and pruritus [25]. Evaluation should access QT interval prolongation and arrhythmogenic cardiotoxicity. While macular toxicity could be a concern in long term treatment, it seems not to be as a relevant concern in short term prophylactic use [21,27].

It is to be hoped that HQ prophylaxis reduce the morbidity and mortality from Covid-19 infection among caregivers, which are particularly exposed and relatively old. If this chemoprophylaxis is proven to be effective, it could also be interesting to access the indication in persons with Covid-19 high risk of mortality, by individually assessing the risk-benefit balance.

### Funding

No funding sources.

### Competing interests

None declared.

### Ethical approval

Not required.

### References

- [1] Winzeler EA. Malaria research in the post-genomic era. *Nature* 2008;455:751–6.
- [2] Parhizgar AR, Tahghighi A. Introducing new antimalarial analogues of chloroquine and amodiaquine: a narrative review. *Iran J Med Sci* 2017;42:115–28.
- [3] Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents* 2020, <http://dx.doi.org/10.1016/j.ijantimicag.2020.105932> [published online 4 March].
- [4] Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents* 2020;55:105923.
- [5] Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents* 2020, <http://dx.doi.org/10.1016/j.ijantimicag.2020.105938> [published online 11 March].
- [6] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.
- [7] Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020;14:72–3.
- [8] Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia [in Chinese]. *Zhonghua Jie He He Hu Xi Za Zhi* 2020;43:185–8.
- [9] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020, <http://dx.doi.org/10.1016/j.ijantimicag.2020.105949> (in press).
- [10] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (covid-19) outbreak in China. Summary of a report of 72314 cases from the Chinese center for disease control and prevention. *JAMA* 2020, <http://dx.doi.org/10.1001/jama.2020.2648> [published online 24 February].
- [11] Aljazeera. Thousands of medical staff infected with coronavirus in Italy. Available at: <https://www.aljazeera.com/news/2020/03/rising-number-medical-staff-infected-coronavirus-italy-200318183939314.html> [updated 23 March 2020].
- [12] CNN. March 20 coronavirus news. Available at: <https://edition.cnn.com/world/live-news/coronavirus-outbreak-03-20-20-intl-hnk/h.0431a207cf2b2b78c7295229b9f6186c> [updated 23 March 2020].

- [13] International Council of Nurses. Press information. Available at: <https://www.icn.ch/news/high-proportion-healthcare-workers-covid-19-italy-stark-warning-world-protecting-nurses-and> [Updated 23 March 2020; accessed 23 March 2020].
- [14] Actu 17. Coronavirus: 345 soignants de l'AP-HP contaminés et 250 patients en réanimation dans les hôpitaux du groupe francilien. Available at: <https://actu17.fr/coronavirus-345-soignants-de-lap-hp-contamines-et-250-patients-en-reanimation-dans-les-hopitaux-du-groupe-francilien/> [Updated 23 March 2020].
- [15] L'Express. Ce que l'on sait sur le premier médecin mort en France à cause du coronavirus. Available at: <https://www.lexpress.fr/actualite/societe/sante/ce-que-l-on-sait-sur-le-premier-medecin-mort-en-france-a-cause-du-coronavirus.2121601.amp.html> [Updated 23 March 2020].
- [16] Le Parisien. Coronavirus: quatre médecins sont morts dans l'Est de la France. Available at: <http://www.leparisien.fr/societe/coronavirus-deux-medecins-sont-morts-dans-le-grand-est-23-03-2020-8285928.php> [Updated 23 March 2020].
- [17] OECD.stat. Médecins par âge et sexe. Available at: <https://stats.oecd.org/Index.aspx?ThemeTreeId=9&lang=fr> [Updated 23 March 2020].
- [18] Ordre National des Médecins. Chiffres clés Médecins inscrits. Available at: [https://www.conseil-national.medecin.fr/sites/default/files/external-package/analyse\\_etude/wbco01/cnom.chiffres.cles.atlas.2018.0.pdf](https://www.conseil-national.medecin.fr/sites/default/files/external-package/analyse_etude/wbco01/cnom.chiffres.cles.atlas.2018.0.pdf) [Updated 23 March 2020].
- [19] L'express. Coronavirus: l'hôpital public face à un risque d'hémorragie de personnel. Available at: <https://www.lexpress.fr/actualite/societe/sante/coronavirus-l-hopital-public-face-a-un-risque-d-hemorragie-de-personnel.2119692.html> [Updated 23 March 2020].
- [20] Financial Times. Exhausted Iranian healthcare workers at risk. Available at: <https://www.ft.com/content/9418125e-6839-11ea-800d-da70c16e4d3> [Updated 23 March 2020].
- [21] Chang R, Sun W. Repositioning chloroquine as ideal antiviral prophylactic against COVID-19 – time is now. Preprints 2020 (doi:10.20944/preprints202003.0279.v1).
- [22] Gouin JP, Hantsoo L, Kiecolt-Glaser JK. Immune dysregulation and chronic stress among older adults: a review. *Neuroimmunomodulation* 2008;15:251–9.
- [23] Ministry of Health and Family Welfare, Government of India. Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. Available at <https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf> [updated 22 April 2020].
- [24] Le quotidien du médecin. Hydroxychloroquine et azithromycine: « Un effet protecteur contre Covid-19 pourrait réduire le flux de patients hospitalisés ». Available at: <https://www.lequotidiendumedecin.fr/actus-medicales/recherche-science/hydroxychloroquine-et-azithromycine-un-effet-protecteur-contre-covid-19-pourrait-reduire-le-flux-de> [updated 22 April 2020].
- [25] Salako LA. Toxicity and side-effects of antimalarials in Africa: a critical review. *Bull World Health Organ* 1984;62 Suppl:63–8.
- [26] Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010;69:20–8.
- [27] Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology* 2016;123:1386–94.