

The Hydroxychloroquine Debate:

A Therapeutic Dilemma for General Practitioners

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Abstract

Purpose

France has been at the epicenter of the worldwide debate about hydroxychloroquine, as the main publications advocating its use to treat COVID-19 come from a research unit led by Didier Raoult in Marseille. The objective of this study was to determine the impact of this debate on the opinions and practices of French primary care physicians.

Methods

At the peak of the pandemic in France, we conducted an online cross-sectional questionnaire survey among a national panel of 2940 self-employed PCPs. The questionnaire assessed their trust in the health authorities, their opinions about the official guidelines for the management of patients with COVID-19, and any difficulties in dealing with these patients requesting prescriptions for hydroxychloroquine.

Results

In all, 1200 PCPs (40.8%) completed the questionnaire. We found that physicians in the areas most strongly affected by the epidemic (40%) or closest to the epicentre of the controversy (50%) reported that the hydroxychloroquine debate had made it difficult for them to deal with patients' treatment requests. Their overall adherence to official recommendations was also lower (RR=0.61). Reported difficulties were less frequent among PCPs in group compared with solo practices (RR=0.67).

Conclusions

The hydroxychloroquine debate created dilemmas for a significant portion of PCPs in a context of undermined trust in the health authorities. In due course, it will be necessary to examine the conditions producing so strong a conflict to ensure better preparation not only for health management but also for knowledge production in the not unlikely event of a future epidemic.

Keywords

COVID-19, coronavirus, primary care, hydroxychloroquine.

Abbreviations

GP: General practitioner

Introduction

Epidemics create a rush for treatment. In this context, the endorsement of pharmaceutical drugs by public figures before proper evaluation can have dire consequences, as was the case with hydroxychloroquine. In the USA, President Trump's unbridled advocacy led to an increase in its off-label sales, shortages for patients with indications for which its efficacy is established, and an increase in its reported cardiac side effects¹. France has been at the epicenter of worldwide debates about this drug, as the main advocacy for its use against COVID-19 have come from a team of infectiologists led by Didier Raoult in Marseille². Hydroxychloroquine's continued prominence in the news since mid-March has persuaded a significant proportion of French public to believe in its efficacy: 48% of them would like to receive the treatment if they were affected³.

The impact of these highly visible debates is not restricted to patients, however. It also affects healthcare providers. Doctors may be affected by patients' requests or demands for a prescription for hydroxychloroquine, or swayed by the arguments presented in favor of its prescription to patients with COVID-19, despite contrary recommendations from the French public health authorities⁴. As studies show, doctors can espouse beliefs at odds with public health authorities' recommendations and scientific consensus on various subjects ranging from vaccination⁵ to Lyme disease⁶.

We conducted a flash survey on COVID-19 among a representative sample of 1200 French self-employed general practitioners (GPs)—who were responsible for diagnosing and managing patients with COVID-19 in the community—to better understand the impact of

controversies of their practices. The present article sought to evaluate the extent to which they may face dilemmas in epidemic contexts where uncertainty is substantial, prominent experts disagree, and medical issues become politicized.

Methods

We used data collected from a national panel of 3300 self-employed GPs established in late 2018. They were randomly selected from the French National Registry of Health Care Workers (Health Ministry). Demographic and professional characteristics of participants were collected at inclusion in the panel. The 2940 GPs (89.1%) still participating in the panel in April 2020 were asked to take this online cross-sectional survey. The questionnaire included the following question: "Does the current controversy over hydroxychloroquine make it difficult for you to respond to requests for treatment by your patients positive for COVID-19?" (yes/no/don't know). It also collected participants' opinions about the official recommendations of the French health authorities on the diagnosis and management of patients with COVID-19: are they clear, sufficient, applicable, or changed too often, 4 items, yes/no, Cronbach alpha=0.66). We weighted data according to GPs' age, gender and workload to obtain a sample representative of this population for these variables.

Results

From April 9 to April 20, 1200 GPs (40.8%) completed the questionnaire. More than 1 doctor in 4 (27%) reported difficulties with their patients due to this polemic. This figure was significantly higher in Southeastern France (50%), where Pr. Raoult's institute is located, and in the areas most affected by the epidemic (40%), compared with 25% in those least affected

(Table 2). This opinion was significantly less frequent in group practices than in solo practices (aRR 0.67, 95% CI 0.49 to 0.90).

Moreover, the official recommendations of the Ministry of Health site for the overall management of patients with suspected or proven Covid-19 infection were clear for 69.5% of the doctors. More than half considered them sufficient (54.7%) or applicable (56.7%), but 64.2% felt that they changed too frequently. Multiple Poisson regression adjusted on age, gender, and region found that overall adherence to these recommendations (score adding up GPs' answers to the 4 items; range 0–4) was significantly lower (aRR 0.61, 95% CI 0.47 to 0.80) among those physicians who felt that the controversy about hydroxychloroquine made it difficult for them to respond to these patients' requests (Table 1).

Discussion

These results are an indicator of the scale of the consequences of the controversy around hydroxychloroquine. Physicians reported more frequent difficulties in the areas most strongly affected by the epidemic and especially those closest to the epicenter of the controversy than elsewhere. In these areas, physicians saw more frequent requests from patients positive for SARS-CoV-2 for the treatment, linked to the hope inspired by the claimed therapeutic benefits of hydroxychloroquine.

More broadly, physicians increasingly face patients who make specific requests or even demands for treatment, based on their own search for information and on non-medical considerations (psychological, cultural, even political with the demand for greater local autonomy). This process of empowerment⁷ through which patients have strengthened their willingness and ability to take effective care of their health has been underway in Western countries for several decades.

The gap between the requests of patients and the guidelines of the health authorities may have created a dilemma among GPs, reinforced by the intensity of the disagreements between experts, the media coverage, and politicization of the debates, as well as the fairly widespread mistrust of the government⁸. Dialogue with colleagues, facilitated in group offices, might have reduced the perception of this dilemma and probably also made it possible to better organize the response to patients' requests for this treatment or medication. Nonetheless, the negative association between the frequency of this problem among physicians and their confidence in the official management guidelines for COVID-19 suggests a second type of explanation. The physicians themselves may sufficiently convinced by the evidence of the hydroxychloroquine defenders to question the official guidelines. Indeed, the debate as it took place in France opposed leading researchers against one another rather than representatives of mainstream science against outsiders; it is therefore different from the controversy about the association between autism and the MMR vaccine that has raged for a decade⁹. On one side were experts who considered it essential to await the results of randomized controlled trials before prescribing hydroxychloroquine to patients with COVID-19. On the other side, Didier Raoult, backed by other medical school professors, claimed that a) the preliminary data and long experience with this substance for the conditions were sufficient to judge its safety, b) an RCT would take too much time and is not appropriate for the production of knowledge for decision-making in emergency situations, and c) the physician's duty is to try to treat the patient. These arguments are particularly likely to have convinced some GPs who in situations of uncertainty would tend to rely on their own judgment rather than clinical practice guidelines¹⁰. Our experience in recent months with physicians in southeastern France shows broad support by GPs, particularly in Marseilles, for the combined therapy recommended by the IHU. Many GPs have taken up the arguments of

the duty to treat (rather than wait for the disease to worsen) and the doctor's freedom to prescribe.

Conclusion

In due course, it will be necessary to examine the conditions producing so strong a conflict and its societal causes as well as its public health and social consequences. This reflection will need to involve all parties, including GPs and not only specialist scientists, to ensure better preparation for health management and for knowledge production in the not unlikely event of a future epidemic.

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Author Contributions

Study concept and design: PV, RL.

Collection of data and data analyses: DC, PV.

Drafting of the manuscript: RL, DC, JW, PV.

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References

1. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19 | Annals of Internal Medicine. URL <https://www.acpjournals.org/doi/full/10.7326/m20-1223> Accessed 6 June 2020.
2. Sayare S. He Was a Science Star. Then He Promoted a Questionable Cure for Covid-19. N. Y. Times. 2020. URL <https://www.nytimes.com/2020/05/12/magazine/didier-raoult-hydroxychloroquine.html> Accessed 6 June 2020.
3. Etude-Coconel-Note-n3-Confinement-masques-chloroquine-vaccin.pdf. URL <https://www.ehesp.fr/wp-content/uploads/2020/04/Etude-Coconel-Note-n3-Confinement-masques-chloroquine-vaccin.pdf> Accessed 6 June 2020.
4. HCSP. Covid-19 : utilisation de l'hydroxychloroquine. Paris: Haut Conseil de la Santé Publique, 2020 URL <https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=837> Accessed 14 June 2020.

5. Wilson RJI, Vergélys C, Ward J, Peretti-Watel P, Verger P. Vaccine hesitancy among general practitioners in Southern France and their reluctant trust in the health authorities. *Int J Qual Stud Health Well-Being* 2020;15:1757336.
6. CNGE. Borréliose de Lyme et autres maladies transmises par les tiques : Pourquoi les sociétés scientifiques et professionnelles refusent de cautionner la recommandation de bonne pratique élaborée par la HAS. 2018.URL https://www.cnge.fr/le_cnge/adherer_cnge_college_academique/cp_cnge_borreliose_de_lyme_et_autres_maladies_tran/ Accessed 1 June 2020.
7. Lupton D. *The Imperative of Health: Public Health and the Regulated Body*. London, 1995 doi:10.4135/9781446221976.
8. Coronavirus : les Français sont les plus sévères d'Europe envers leurs dirigeants. URL <https://www.lefigaro.fr/politique/coronavirus-les-francais-sont-les-plus-severes-d-europe-envers-leurs-dirigeants-20200510> Accessed 14 June 2020.
9. Dubé E, Vivion M, MacDonald NE. Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. *Expert Rev Vaccines* 2015;14:99–117.
10. Bloy G. L'incertitude en médecine générale : sources, formes et accommodements possibles. *Sci Soc Sante* 2008;Vol. 26:67–91.

Table 1. Factors associated, among general practitioners, with agreement that the controversy over hydroxychloroquine made it difficult for them to deal with requests for the treatment from patients who tested positive for COVID-19, modified Poisson regression, weighted data, April 2020 (Ref. Do not agree, N=1151)

Factors	aRR	95% CI
Sex (ref. Male)		
Female	1.16	[0.87,1.55]
Region (ref. Rest of France)		
South-eastern France	2.10***	[1.58,2.80]
Western France (Pays de la Loire)	0.86	[0.58,1.27]
Intensity of the Covid-19 epidemic in French districts (ref. Low)		
Moderate	1.14	[0.77,1.70]
High	1.79**	[1.17,2.74]
Age (ref. < 50 years old)		
50-59	0.80	[0.55,1.15]
>= 60	0.94	[0.66,1.33]
General Practitioners density (ref. low)		
Yes	1.18	[0.86,1.61]
Type of practice (ref. solo)		
Group	0.67**	[0.49,0.90]
Workload (ref. Min-Q1)		
Q1-Q3	1.03	[0.76,1.41]
Q3-Max	1.23	[0.85,1.78]
Score of trust in the Health Ministry to manage the Covid-19 epidemic [0-12] (ref. Low [0-7])		
High [8-12]	0.80	[0.59,1.09]
P-value: * < 0.05 ; ** < 0.01 ; *** < 0.001		