

RESEARCH ARTICLE

Outside any therapeutic trial prescription of hydroxychloroquine for hospitalized patients with covid-19 during the first wave of the pandemic: A national inquiry of prescription patterns among French hospitalists

Antoine Bosquet^{1*}, Comlan Affo¹, Ludovic Plaisance², Géraldine Poenou², Emmanuel Mortier³, Isabelle Mahé^{2,4}

1 Assistance-Publique—Hôpitaux de Paris (AP-HP), DMU ESPRIT, Service de Médecine Interne, Hôpital Louis-Mourier, Université de Paris, Colombes, France, **2** Université de Paris, Assistance-Publique—Hôpitaux de Paris (AP-HP), DMU ESPRIT, Service de Médecine Interne, Hôpital Louis-Mourier, Colombes, France, **3** Assistance-Publique—Hôpitaux de Paris (AP-HP), DMU ESPRIT, Polyclinique, Hôpital Louis-Mourier, Colombes, France, **4** Inserm UMR_S1140, Innovative Therapies in Haemostasis Paris, Paris, France

* antoine.bosquet@aphp.fr



OPEN ACCESS

Citation: Bosquet A, Affo C, Plaisance L, Poenou G, Mortier E, Mahé I (2022) Outside any therapeutic trial prescription of hydroxychloroquine for hospitalized patients with covid-19 during the first wave of the pandemic: A national inquiry of prescription patterns among French hospitalists. PLoS ONE 17(1): e0261843. <https://doi.org/10.1371/journal.pone.0261843>

Editor: Abdelwahab Omri, Laurentian University, CANADA

Received: June 25, 2021

Accepted: December 10, 2021

Published: January 21, 2022

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0261843>

Copyright: © 2022 Bosquet et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Introduction

During the first wave of the coronavirus-disease 2019 (covid-19) pandemic in early 2020, hydroxychloroquine (HCQ) was widely prescribed in light of in vitro activity against severe acute respiratory syndrome—coronavirus-2 (SARS-CoV-2). Our objective was to evaluate in early 2020 the rate of French hospitalists declaring having prescribed HCQ to treat covid-19 patients outside any therapeutic trial, compare the reasons and the determinants for having prescribed HCQ or not.

Material and methods

A national inquiry submitted by email from May 7 to 25, 2020, to a sample of French hospitalists: doctors managing patients hospitalized for covid-19 in a French department of internal medicine or infectious diseases and identified in the directories of French hospitals or as a member of the French Infectious Diseases Society (SPILF). Primary outcome was the percentage of hospitalists declaring having prescribed HCQ to covid-19 patients. Secondary outcomes were reasons and determinants of HCQ prescription.

Results

Among 400 (22.8%) responding hospitalists, 45.3% (95% CI, 40.4 to 50.1%) declared having prescribed HCQ to covid-19 patients. Two main profiles were discerned: HCQ prescribers who did not raise its efficacy as a motive, and non-prescribers who based their decision on evidence-based medicine. Multivariate analysis retained the following prescription determinants (adjusted odds ratio; 95% confidence interval): a departmental procedure for HCQ

Data Availability Statement: All relevant data are within the paper and its [Supporting Information](#) files.

Funding: The author(s) received no specific funding for this work.

Competing interests: Dr. Mahé reports grants from BMS Pfizer, grants from LEO Pharma, personal fees and non-financial support from BMS Pfizer, personal fees and non-financial support from Leo Pharma, personal fees and non-financial support from Bayer, outside the submitted work. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

prescription (8.25; 4.79 to 14.20), having prescribed other treatments outside a therapeutic trial (3.21; 1.81 to 5.71), prior HCQ prescription (2.75; 1.5 to 5.03) and HCQ prescribed within the framework of a therapeutic trial (0.56; 0.33 to 0.95).

Conclusion

Almost half of the hospitalists prescribed HCQ. The physician's personality (questioning or not evidence-based–medicine principles in the context of the pandemic) and departmental therapeutic procedures were the main factors influencing HCQ prescription. Establishment of “therapeutic” procedures represents a potential means to improve the quality of therapeutic decision-making during a pandemic.

Introduction

By March 2021, the coronavirus-disease 2019 (covid-19) pandemic had affected more than 120 million persons worldwide and had led to more than 2.5 million deaths [1]. Despite the rapid initiation of numerous therapeutic trials [2], no antiviral treatment had proven efficacy in 2020 [3]. Chloroquine and hydroxychloroquine (HCQ) were the first drugs proposed to treat covid-19 in light of their *in vitro* activity against severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) [4] that causes covid-19. HCQ has been used for decades to treat malaria and autoimmune diseases with a good safety profile and is inexpensive. At the start of 2020, the results of some studies suggested that HCQ might be effective against SARS-CoV-2 [5,6]. In the emergency context and without proof of its efficacy, HCQ was recommended in the national policies of many countries, notably emerging nations [7]. HCQ use was the object of numerous debates among caregivers and the public at large [8,9]. Results of physician surveys [10–12], analysis of HCQ prescriptions filled in city pharmacies [13–15] and observational in-hospital studies (S1 Table) showed that HCQ was widely prescribed worldwide during the first wave of the covid-19 pandemic in early 2020. However, no specific data on doctors' reasons and determinants for prescribing HCQ in-hospital were available.

On 25 March 2020, French government authorized HCQ use only for hospitalized patients, after informed consent had been obtained and based on a collegial decision [16]. Because that authorization was in no way a recommendation, it remains to assess the attitudes and opinions of hospitalists.

The primary objective was to determine the percentage of internal medicine or infectious disease hospitalists declaring having started HCQ outside a therapeutic trial to manage covid-19 patients. Secondary aims were to analyze the reasons the hospitalists gave for having prescribed HCQ or not, and what determined that decision.

Materials and methods

Design of the study

Questionnaire. We built a questionnaire that was drafted, stored and available on Google Form® (S1–S3 Appendices). The first versions of the questionnaire were tested on departmental hospitalists (IM, LP, LA, JC, SD) to evaluate comprehension of the items and the time needed to complete the inquiry. The questionnaire consists of 68 questions: 25 were asked of all participants, 43 only to some according to their previous answers, with the total number

varying from 37 to 62. A link to the electronic questionnaire was sent by e-mail starting May 1, 2020, with reminders sent at 1-week intervals, and closure May 25, 2020.

Participating hospitalists. The population targeted was defined as hospitalists managing covid-19 patients and practicing in France in a department of internal medicine or infectious disease, and entered in the directories of French hospitals ($n = 1387$) [17,18] or members of the French Infectious Diseases Society (SPILF) ($n = 572$). After the exclusion of 80 duplicates, the questionnaire was sent to 1879 hospitalists. Each participant provided written consent prior to gaining access to the questionnaire. Participants were not paid.

Declaration to the French Computer Watchdog Commission (CNIL)

The agreement of conformity of the study was obtained from the CNIL on April 20, 2020 (no. 2217633 v 0).

Statistical methods

The analysis considered two groups of hospitalists: one was composed of those who reported having started HCQ for a patient outside a clinical trial at least once (henceforth called prescribers); the other group (non-prescribers) included physicians who declared not having initiated HCQ, except within the framework of a therapeutic trial.

Continuous variables are reported as mean \pm standard deviation (SD). Categorical variables are reported as number (percentages; which were calculated excluding missing data). Every relevant proportion is accompanied by its 2-sided 95% confidence interval (Wilson method). Missing data were not handled. A logistic-regression model assessed HCQ-prescription determinants. First, univariate analyses ($p < 0.2$) selected potential explanatory variables that were then entered into the multivariate model (stepwise method with entry/stay significance levels of 0.2/0.05). The results are expressed as adjusted odd ratios (aOR) with their 95% confidence intervals. Due to the heterogeneity of the numbers of physicians per region (6 regions had $< 5\%$ of the sample), to analyze the variable region in the logistic-regression model, the 13 metropolitan regions (exclusion of the three physicians from overseas departments) were grouped into five geographical areas: Île-de-France, Northeast (Bourgogne-Franche-Comté, Grand Est, Hauts-de-France), Northwest (Normandy, Brittany, Centre-Val de Loire, Pays de la Loire), Southwest (Nouvelle-Aquitaine, Occitanie) and Southeast (Auvergne-Rhône-Alpes, Provence-Alpes-Côte d'Azur, Corsica). Pearson's correlation coefficient and its 95% confidence interval were used to assess the relationship between the HCQ-prescription rate and cumulative in-hospital-mortality rate per region. A p -value < 0.05 was considered significant, unless specified otherwise. All statistical analyses were performed with SAS release 9.4 (SAS Institute Inc, Cary, NC) statistical software package.

Results

Among the 1879 to whom the questionnaire was sent, 127 were not received (distribution error message received after sending), 400 hospitalists completed the entire questionnaire, for a response rate of 22.8% (400/1752).

Responders' characteristics

The demographic characteristics of the responders who completed the questionnaire are reported in Tables 1 and S2.

Table 1. Participating hospitalists' characteristics.

Characteristic	HCQ prescription for covid-19 patients		
	Total, n (%)	Yes, n (%)	No, n (%)
Sex			
n	400	181	219
Male	208 (52)	87 (48.1)	121 (55.3)
Female	192 (48)	94 (51.9)	98 (44.7)
Years in practice, n			
n	400	181	219
0–4	66 (16.5)	30 (16.6)	36 (16.4)
5–9	76 (19)	32 (17.7)	44 (20.1)
10–19	91 (22.8)	43 (23.8)	48 (21.9)
20–29	99 (24.8)	51 (28.2)	48 (21.9)
≥30	68 (17)	25 (13.8)	43 (19.6)
Hospital type			
n	400	181	219
Private	22 (5.5)	12 (6.6)	10 (4.6)
Teaching public	210 (51.5)	89 (49.2)	121 (55.3)
Non-teaching public	168 (42)	80 (44.2)	88 (40.2)
Specialty			
n	400	181	219
Other specialties	91 (22.8)	33 (18.2)	58 (26.5)
Infectious diseases (ID)	144 (36)	58 (32.0)	86 (39.3)
Internal medicine (IM)	137 (34.3)	73 (40.3)	64 (29.2)
ID & IM	28 (7)	17 (9.4)	11 (5.0)
Hospital region			
n	400	181	219
Auvergne Rhône-Alpes	37 (9.3)	21 (11.6)	16 (7.3)
Bourgogne-Franche-Comté	24 (6.0)	15 (8.3)	9 (4.1)
Brittany	10 (2.5)	0 (0.0)	10 (4.6)
Centre-Val de Loire	16 (4.0)	6 (3.3)	10 (4.6)
Grand Est	58 (14.5)	19 (10.5)	39 (17.8)
Hauts-de-France	34 (8.5)	7 (3.9)	27 (12.3)
Île-de-France	109 (27.3)	61 (33.7)	48 (21.9)
Normandy	20 (5.0)	14 (7.7)	6 (2.7)
Nouvelle-Aquitaine	24 (6.0)	10 (5.5)	14 (6.4)
Occitanie	18 (4.5)	7 (3.9)	11 (5.0)
Pays de la Loire	18 (4.5)	3 (1.7)	15 (6.8)
Provence-Alpes-Côte d'Azur & Corsica	29 (7.3)	17 (9.4)	12 (5.5)
Overseas departments	3 (0.8)	1 (0.6)	2 (0.9)
Previous HCQ prescription			
n	398	181	217
No	89 (22.4)	28 (15.5)	61 (28.1)
Yes	309 (77.6)	153 (84.5)	156 (71.9)

<https://doi.org/10.1371/journal.pone.0261843.t001>

HCQ was started to treat covid-19 by 45.3% of the hospitalists (95% CI, 40.4–50.1%); 93.6% (205/219) of the remaining responders never prescribed HCQ to their covid-19 patients, but 6.4% (14/219) sometimes continued HCQ prescribed by colleagues.

Physicians reasons for prescribing HCQ or not

Hospitalists' most frequently chosen reasons for prescribing HCQ (Table 2) were the only therapeutic option available (no alternative; 56.9%), application of a collegial decision (50.8%), the favorable HCQ safety profile (49.7%), the potential severity of covid-19 (48.6%). About a third of the hospitalists recognized the uncertainty of HCQ efficacy, while only 13.8% declared having prescribed HCQ because "HCQ seemed effective". For 10% (n = 19, 95% CI, 6.8 to 15.8%) of the responders, the prescription continued a third-party decision, the only reason for prescription was either "I applied a collegial decision" or "It was requested by the patients and/or his/her entourage" (n = 4).

Overall, 84.5% (95% CI, 79.1 to 88.7%) of non-prescribers justified their choice by at least one of the following reasons (Table 2): "No indication according to the available medicine/science-based" (74.4%), "Consider it unethical to prescribe a drug that is not validated outside therapeutic trials" (35.6%), "opposed to off-label prescription" (4.6%) "No official recommendations supporting HCQ prescription" (50.7%). The remaining non-prescribers (15.5%) had practical reasons: no collegial discussion was organized in their department or patients did not meet the criteria for prescription. In addition, ~36% of non-prescribers feared potential adverse events of HCQ or covid-19 worsening under HCQ (5.5%).

Determinants of HCQ prescription

Univariate analyses identified factors associated with HCQ prescription (Tables 3 and S3). The most important was an established departmental procedure that increased HCQ prescriptions (8.36 [5.12 to 13.65]). That protocol indicated that HCQ should be prescribed to all (3%), certain (88%) or no patients (9%). Previous HCQ prescription, media pressure and the advice of colleagues also influenced HCQ prescription. Although 43.3% (95% CI, 38.5 to 48.1%) of the responders indicated that their HCQ prescription was influenced by the media pressure, that effect seemed somewhat variable: more prescriptions for 38.2% of the prescribers, fewer for 7.6% of them and 23.3% of non-prescribers. In contrast, no links were found between HCQ prescription and the intensity of the epidemic according to the region (S1 Fig, S4 Table), the physicians' sex, the duration of his/her practicing medicine or the type of hospital (university or not).

The multivariable analysis retained the following criteria as being significantly and independently associated with HCQ prescription (Table 3): an established departmental HCQ-prescription procedure (aOR, 8.25, 95% CI, 4.79 to 14.2; $P < 0.0001$), previously prescribed HCQ (aOR, 2.75, 95% CI, 1.5 to 5.03; $P = 0.001$), outside a therapeutic trial prescription of drugs other than HCQ to treat covid-19 (aOR, 3.21, 95% CI, 1.81 to 5.71; $P < 0.0001$).

Discussion

This nationwide inquiry, conducted during the first wave of the covid-19 pandemic in France, addressing HCQ prescription, found that 45.3% of the responding hospitalists declared having prescribed HCQ to covid-19 patients outside any therapeutic trial. Two profiles could be discerned, distributed almost equally: prescribers, among whom only 13.8% based their decision on HCQ efficacy; and non-prescribers, among whom 85% relied on relevant evidence-based medicine (EBM) criteria to support their position. Our multivariate analysis retained the following as reasons being independently associated with prescribing HCQ: a departmental HCQ-prescription procedure, outside a therapeutic trial prescription of other treatments, prior HCQ prescription and no HCQ prescription within the framework of a therapeutic trial.

Table 2. Physicians reasons for prescribing HCQ or not.

Reason	Hospitalists, n (%)	95% CI†
For prescription (multiple choice)		
	HCQ prescribers (N = 181)	
Only therapeutic option available (no alternative)	103 (56.9)	49.6 to 63.9
You applied the recommendation of the collegial decision	92 (50.8)	43.6 to 58
It is an old drug with a known, favorable safety profile	90 (49.7)	42.5 to 56.9
Covid-19 is a potentially very serious disease	88 (48.6)	41.4 to 55.9
HCQ efficacy against covid-19 was not certain but usual rules for drugs are not applicable during a public health emergency	64 (35.4)	28.8 to 42.6
Its prescription was made possible by a health ministry decree	51 (28.2)	22.1 to 35.1
HCQ is an inexpensive and available drug	51 (28.2)	22.1 to 35.1
Requested by the patient or his/her entourage	37 (20.4)	15.2 to 26.9
HCQ seems to be effective against covid-19	25 (13.8)	9.5 to 19.6
It seemed difficult to resist media pressure	17 (9.4)	5.9 to 14.5
It was recommended by colleagues	13 (7.2)	4.2 to 11.9
It was recommended by “medical authorities”	10 (5.5)	3.0 to 9.9
Fear of medical–legal consequences	4 (2.2)	0.9 to 5.5
Fear of the how I would be viewed by my departmental colleagues	4 (2.2)	0.9 to 5.5
The patient had already taken HCQ for another indication	2 (1.1)	0.3 to 3.9
Not to prescribe HCQ (multiple choice)		
	HCQ non-prescribers (N = 219)	
No indication according to currently available medicine/science data	163 (74.4)	68.3 to 79.8
Absence of official recommendation* supporting HCQ prescription	111 (50.7)	44.1 to 57.2
Fear of potential adverse events	79 (36.1)	30.3 to 42.6
You think it unethical to prescribe a non-validated drug outside therapeutic trials	78 (35.6)	29.6 to 42.2
None of your patients met the criteria for HCQ prescription established in your department	21 (9.6)	6.4 to 14.2
Fear that HCQ could contribute to covid-19 worsening	12 (5.5)	3.2 to 9.3
You are opposed to off-label prescription	10 (4.6)	2.5 to 8.2
No collegial organized discussion or in your department	9 (4.1)	2.2 to 7.6
You didn’t even consider its prescription	7 (3.2)	1.6 to 6.4
Fear of medical–legal consequences	5 (2.3)	1.0 to 5.2

(Continued)

Table 2. (Continued)

Fear of the reactions or opinions of your colleagues	4 (1.8)	0.7 to 4.6
Refusal of the patient or his/her entourage	3 (1.4)	0.5 to 3.9

* Learned societies, the Academy of Medicine, National Association of Physicians.

† IC 95% values are percentages of respondents.

<https://doi.org/10.1371/journal.pone.0261843.t002>

Percentage of HCQ prescribers

The observed prescriber rate (45.3%) was higher than in certain French (14%) [11] or international (12%) [19] inquiries, but lower than in others (90%) [12]. The differences can be explained by the specific prescription context (outpatient) [19], the country [12] or the time of the inquiries [19]. In the recurrent Sermo international inquiries, the mean prescriber rate was comparable to ours and varied over time: it increased from 33% to 58% from March to April 2020 (in-hospital or private practice), then declined from 66% to 28% from April to July (in-hospital practice exclusively) [10]. Those inquiries had methodological weaknesses: prescription context not always specified (in-hospital or private practice) [11], representativity of the responders unknown because of the selection method [10–12,19]. A high rate of HCQ prescription during the first wave of the pandemic has been associated by some authors with possible risks: toxicity [20–22], depletion of stocks [19,23] or deterring research [24,25]. Others suggest that HCQ may have been beneficial for patients hospitalized for Covid-19 (S1 Table). In any case, our study showed that French hospitalists were very divided on the prescription of HCQ during the first wave of covid-19 pandemic. This confirms the interest of an ethical reflection on the prescription of unproven interventions outside research in a pandemic period, such as that initiated by the WHO [26]. The examples against HCQ (unconfirmed efficacy as during Chikungunya virus infection) [3,27,28] and corticosteroids (efficacy discussed a priori [29], confirmed a posteriori) [30] illustrate the difficulty of this exercise.

Physicians reasons for prescribing HCQ or not

The majority of prescribers seem to be aware that the effectiveness of HCQ has not been established: they used HCQ without citing efficacy as a criterion. They justifies their attitude by HCQ favorable tolerance profile or the disease severity, which are known prescription criteria, with others declared criteria: availability, price and regulatory context of HCQ prescription [31,32]. This attitude can evoke the prescription profile called “just do it” by Aquino and Cabrera in the context of the pandemic emergency, during which no specific treatment had proven efficacy [33]: prescribe treatments with unevaluated effects hoping for a favorable benefit/risk ratio but taking the risk of drugs being ineffective or even deleterious [34]. Furthermore, a clear majority (85%) of non-prescriber hospitalists explained their decisions citing relevant EBM criteria. A third of them declared they were afraid of potential adverse effects, seeming to adhere to the “first, do no harm” principle, even if that meant not prescribing a therapy that might later prove effective [33,34].

Determinants of HCQ prescription

Our results confirmed that the HCQ-prescription rate differed according to the physician’s specialty [35] or geographical region [10,15,19] but not according to the number of years of experience, unlike Baicus et al and Mehta et al [28,36]. But this association was not retained by multivariate analysis, not performed in others studies [10,15,19,35,36]. That finding held true

Table 3. Univariate and multivariate analyses of HCQ-prescription determinants.

Determinant	Univariate analysis*		Multivariate analysis*	
	aOR [95% CI]	P value	aOR [95% CI]	P value
Sex				
Male	1			
Female	0.75 [0.51 to 1.11]	0.1526		
Years in practice, n				
0–4	1			
5–9	0.87 [0.45 to 1.7]	0.6882		
10–19	1.08 [0.57 to 2.03]	0.8236		
20–29	1.27 [0.68 to 2.38]	0.4458		
≥30	0.7 [0.35–1.39]	0.3073		
Specialty				
Other specialty	1			
Infectious diseases (ID)	1.19 [0.69 to 2.04]	0.5385		
Internal medicine (IM)	2 [1.16 to 3.45]	0.0121		
ID & IM	2.72 [1.14 to 6.49]	0.0245		
Hospital type				
Private	1			
Teaching public	0.61 [0.25 to 1.48]	0.2771		
Non-teaching public	0.76 [0.31 to 1.85]	0.5419		
Hospital geographical region†				
Paris region	1			
Northwest	0.44[0.23 to 0.83]	0.0117		
Northeast	0.43 [0.25 to 0.74]	0.0021		
Southwest	0.54 [0.26 to 1.1]	0.0900		
Southeast	1.07 [0.58 to 1.98]	0.8348		
Previous HCQ prescription				
No	1			
Yes	2.14 [1.3 to 3.52]	0.0029	2.75 [1.5 to 5.03]	0.001
HCQ procedure				
No	1			
Yes	8.36 [5.12 to 13.65]	<0.001	8.25 [4.79 to 14.2]	< .0001
Outside a therapeutic trial prescription (others/HCQ)§				
No	1			
Yes	3.74 [2.3 to 6.07]	<0.001	3.21 [1.81 to 5.71]	< .0001
HCQ prescription in therapeutic trial				
No	1			
Yes	0.68 [0.45 to 1.03]	0.0707	0.56 [0.33 to 0.95]	0.0301
Other prescriptions in therapeutic trials				
No	1			
Yes	0.84 [0.56 to 1.28]	0.4242		
Sensitive to media pressure				
No	1			
Yes	1.55 [1.04 to 2.32]	0.0301		

*Univariate analyses ($P < 0.2$) selected potential explanatory variables that were then tested in the multivariate model (stepwise method with entry/stay significance levels of 0.2/0.05). The results are expressed as adjusted odd ratios (aOR) [95% confidence interval (CI)].

†Northwest: Normandy, Brittany, Centre-Val de Loire and Pays de la Loire; Northeast: Bourgogne-Franche-Comté, Grand Est and Hauts-de-France, Southwest: Nouvelle-Aquitaine and Occitanie; Southeast: Auvergne-Rhône-Alpes, Provence-Alpes-Côte d'Azur and Corsica.

§Lopinavir/ritonavir, Remdesivir, interleukin (IL)-6 inhibitors and/or IL-1 inhibitors, convalescent plasma, corticosteroids or others.

<https://doi.org/10.1371/journal.pone.0261843.t003>

for the region and the specialty (internal medicine), probably partially because of the significant rate of internists who had previously prescribed HCQ before the covid-19 pandemic.

Among the determinants retained by the multivariate analysis, the existence of HCQ-prescription procedures was the factor the most strongly associated with HCQ prescription. Procedure existence per se could have incited hospitalists to prescribe HCQ. Moreover, departments that established procedures might have had more physicians favorable to HCQ use. The establishment of in-hospital procedures could enhance a sense of adequacy between healthcare practices and EBM [37,38]. No specific work on this question during a pandemic was found, other than a moderate-quality study of clinical guidelines published at the onset of the pandemic [39] and contribution of living guidelines [3].

The association between HCQ prescription in therapeutic trials and less HCQ prescription outside a therapeutic trial, as herein, could support the hypothesis that the HCQ prescription depends on the personality of the hospitalist: non prescribers are more likely to support EBM despite the pandemic context. But limiting that association to therapeutic trials on HCQ might simply illustrate that, for the departments that established therapeutic trials on HCQ, the hospitalists preferred including patients in trials rather than prescribe outside one. Moreover, the fact that HCQ prescribers declared prescribing, more often as non-prescribers, other treatments of non-proven efficacy against covid-19 indicates that their prescribing attitude is not specific to HCQ and to a more general tendency to prescribe treatments with unproven efficacy in times of pandemic, adopting a “just do it” profile [33,34]. Doctors experienced in using HCQ for another indication had more HCQ prescriptions for covid-19. Indeed, prior experience with a drug is a known factor for prescription [31]. This finding could reflect a cognitive bias [40].

While the link between poor-quality medical publications, media repercussions, and HCQ-prescription policies [8,13,15,35,41,42] or more HCQ prescriptions [13,15,35] has been reported, our multivariate analysis did not retain media pressure as being associated with increased HCQ prescription.

Strengths and limitations of this study

To our knowledge, no other study has evaluated the HCQ-prescription rate and reasons for its prescription during the pandemic of a well-characterized population of French internal medicine or infectious disease hospitalists. Moreover, responders estimated the mean overall quality of the questionnaire to be 7.2 (± 1.2)/10.

The timing of the inquiry (May 2020) during the first wave of the covid-19 pandemic in France (February to May 2020) enabled assessment of HCQ prescription. This choice might also have biased certain responses. However, after the inclusion period no randomized trial results on a large population were available [43] and both French and World Health Organization (WHO) public health authority released recommendations toward HCQ use to treat covid-19 only within therapeutic trial [44,45].

Our study has several limitations. The response rate was only 22.8%, but nevertheless close to other inquiries on HCQ use during the pandemic: 17% (1215/7000) [12], 29% (785/2645) [36], or 27% (71/260) [46]. Our study was declarative, which could have partially impacted the results. Our inquiry was sent exclusively to internal medicine and infectious disease departments, so the findings cannot be extrapolated to other departments that could have prescribed HCQ, eg, geriatrics or intensive care.

Conclusions

This study provides information on in-hospital HCQ prescription outside any therapeutic trial in France during the first wave of the covid-19 pandemic: its high frequency, varied practices

of the hospitalists according to each one's questioning of EBM principles because of the pandemic, the influence of codified hospital procedures. Understanding the modalities of hospitalists' therapeutic decision-making during the pandemic would be a first step towards subsequently optimizing therapeutic decision-making processes. The existence of prescription procedures was the factor the most strongly associated with HCQ prescription herein. Nonetheless, our findings suggest that prescription procedures during the pandemic is a way to improve the quality of therapeutic decisions. Notably, such protocols, elaborated by independent authorities, based on robust scientific data and up-dated according to validated procedures could help physicians provide better care of their patients.

Supporting information

S1 Fig. Correlation between the in-hospital hydroxychloroquine prescription rate and cumulative in-hospital-mortality rate according to French geographic region during the first semester of 2020, ie, the first wave of covid-19.

(DOCX)

S1 Table. Observational studies of off-label HCQ prescription for hospitalized covid-19 patients in real-life.

(DOCX)

S2 Table. Comparison of participants' specialties.

(DOCX)

S3 Table. HCQ-prescription determinants: Sources of information on HCQ to treat covid-19.

(DOCX)

S4 Table. Cumulative in-hospital-mortality rate per 100,000 inhabitants linked to covid-19 on May 7, 2020 in France.

(DOCX)

S1 Appendix. Inquiry questionnaire (French).

(DOCX)

S2 Appendix. Inquiry questionnaire (English).

(DOCX)

S3 Appendix. Checklist for Reporting Results of Internet E-Surveys (CHERRIES).

(DOCX)

S1 File.

(XLSX)

Acknowledgments

We sincerely thank all the doctors who took the time to complete the questionnaire. The authors also thank Pierre Tattevin, president of the French Infectious Diseases Society (SPLIF), for having accepted to send the questionnaire via email to Society members. The authors thank Stéphanie Rouanet (StatEthic SASU) for the statistical analyses and Janet Jacobson for editorial assistance.

Author Contributions

Conceptualization: Antoine Bosquet, Comlan Affo, Isabelle Mahé.

Data curation: Antoine Bosquet.

Formal analysis: Antoine Bosquet, Comlan Affo, Isabelle Mahé.

Investigation: Antoine Bosquet.

Methodology: Antoine Bosquet, Comlan Affo, Ludovic Plaisance, Isabelle Mahé.

Project administration: Antoine Bosquet.

Resources: Antoine Bosquet.

Supervision: Antoine Bosquet.

Validation: Antoine Bosquet, Comlan Affo, Emmanuel Mortier, Isabelle Mahé.

Visualization: Antoine Bosquet, Isabelle Mahé.

Writing – original draft: Antoine Bosquet, Comlan Affo, Emmanuel Mortier.

Writing – review & editing: Antoine Bosquet, Comlan Affo, Ludovic Plaisance, Géraldine Poenou, Emmanuel Mortier, Isabelle Mahé.

References

1. WHO Coronavirus (COVID-19) Dashboard. [cited 11 Mar 2021]. Available: <https://covid19.who.int>.
2. Cheng MP, Lee TC, Tan DHS, Murthy S. Generating randomized trial evidence to optimize treatment in the COVID-19 pandemic. *CMAJ Can Med Assoc J J Assoc Medicale Can.* 2020; 192: E405–E407. <https://doi.org/10.1503/cmaj.200438> PMID: 32336678
3. Siemieniuk R, Rochwerg B, Agoritsas T, Lamontagne F, Leo Y-S, Macdonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ.* 2020; 370: m3379. <https://doi.org/10.1136/bmj.m3379> PMID: 32887691
4. Hernandez AV, Roman YM, Pasupuleti V, Barboza JJ, White CM. Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19. *Ann Intern Med.* 2020; 173: 287–296. <https://doi.org/10.7326/M20-2496> PMID: 32459529
5. Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. [A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19]. *Zhejiang Xue Xue Bao Yi Xue Ban J Zhejiang Univ Med Sci.* 2020; 49: 215–219. <https://doi.org/10.3785/j.issn.1008-9292.2020.03.03> PMID: 32391667
6. Yu B, Li C, Chen P, Zhou N, Wang L, Li J, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. *Sci China Life Sci.* 2020; 63: 1515–1521. <https://doi.org/10.1007/s11427-020-1732-2> PMID: 32418114
7. Belayneh A. Off-Label Use of Chloroquine and Hydroxychloroquine for COVID-19 Treatment in Africa Against WHO Recommendation. *Res Rep Trop Med.* 2020; 11: 61–72. <https://doi.org/10.2147/RRTM.S269936> PMID: 32982538
8. Kim AHJ, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-García A, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. *Ann Intern Med.* 2020; 172: 819–821. <https://doi.org/10.7326/M20-1223> PMID: 32227189
9. Liu M, Caputi TL, Dredze M, Kesselheim AS, Ayers JW. Internet Searches for Unproven COVID-19 Therapies in the United States. *JAMA Intern Med.* 2020; 180: 1116–1118. <https://doi.org/10.1001/jamainternmed.2020.1764> PMID: 32347895
10. Breaking Results: Sermo's COVID-19 Real Time Global Barometer. In: app.sermo.com/covid19-barometer [Internet]. [cited 11 Mar 2021]. Available: <https://app.sermo.com/covid19-barometer>.
11. Impact de la crise du Covid sur l'éthique médicale: résultats d'enquête. In: *Medscape* [Internet]. [cited 11 Mar 2021]. Available: <https://français.medscape.com/diaporama/33000220>.
12. Attanasi M, Pasini S, Caronni A, Pellegrino GM, Favero P, Di Pillo S, et al. Inpatient Care during the COVID-19 Pandemic: A Survey of Italian Physicians. *Respir Int Rev Thorac Dis.* 2020; 99: 667–677. <https://doi.org/10.1159/000509007> PMID: 32756065
13. Vaduganathan M, van Meijgaard J, Mehra MR, Joseph J, O'Donnell CJ, Warraich HJ. Prescription Fill Patterns for Commonly Used Drugs During the COVID-19 Pandemic in the United States. *JAMA.* 2020; 323: 2524–2526. <https://doi.org/10.1001/jama.2020.9184> PMID: 32463459

14. Shehab N, Lovegrove M, Budnitz DS. US Hydroxychloroquine, Chloroquine, and Azithromycin Outpatient Prescription Trends, October 2019 Through March 2020. *JAMA Intern Med.* 2020; 180: 1384–1386. <https://doi.org/10.1001/jamainternmed.2020.2594> PMID: 32628242
15. Usage des médicaments de ville en France durant l'épidémie de Covid-19: point de situation à la fin du confinement—Point d'Information—ANSM: Agence nationale de sécurité du médicament et des produits de santé. [cited 11 Mar 2021]. Available: <https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Usage-des-medicaments-de-ville-en-France-durant-l-epidemie-de-Covid-19-point-de-situation-a-la-fin-du-confinement-Point-d-Information>.
16. Décret n° 2020–314 du 25 mars 2020 complétant le décret n° 2020–293 du 23 mars 2020 prescrivant les mesures générales nécessaires pour faire face à l'épidémie de covid-19 dans le cadre de l'état d'urgence sanitaire—Légifrance. [cited 11 Mar 2021]. Available: <https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000041755775/>.
17. Annuaire hospitalier et médico-social FHF—Fédération Hospitalière de France (FHF). [cited 11 Mar 2021]. Available: <https://etablisements.fhf.fr/annuaire/>.
18. 32 CHRU—Réseau CHU, l'actualité des CHU. [cited 11 Mar 2021]. Available: <https://www.reseau-chu.org/32-chru/>.
19. Mehta B, Moezinia CJ, Jannat-Khah D, Gibofsky A, Tornberg H, Pearce-Fisher D, et al. Hydroxychloroquine and Chloroquine in COVID-19: A Survey of Prescription Patterns Among Rheumatologists. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis.* 2020; 26: 224–228. <https://doi.org/10.1097/RHU.0000000000001539> PMID: 32694358
20. Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2021; 27: 19–27. <https://doi.org/10.1016/j.cmi.2020.08.022> PMID: 32860962
21. Axfors C, Schmitt AM, Janiaud P, van't Hooft J, Abd-Elsalam S, Abdo EF, et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. *Nat Commun.* 2021; 12: 2349. <https://doi.org/10.1038/s41467-021-22446-z> PMID: 33859192
22. COVID-19—Dispositif renforcé de Pharmacovigilance et d'Addictovigilance—ANSM: Agence nationale de sécurité du médicament et des produits de santé. [cited 11 Mar 2021]. Available: [https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Systemes-de-vigilances-de-l-Agence/COVID-19-Dispositif-renforce-de-Pharmacovigilance-et-d-Addictovigilance/\(offset\)/0https://www.ansm.sante.fr/content/download/183671/2402443/version/1/file/20200930_Rapport-Enquete-COVID-n15.pdf](https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Systemes-de-vigilances-de-l-Agence/COVID-19-Dispositif-renforce-de-Pharmacovigilance-et-d-Addictovigilance/(offset)/0https://www.ansm.sante.fr/content/download/183671/2402443/version/1/file/20200930_Rapport-Enquete-COVID-n15.pdf).
23. Michaud K, Wipfler K, Shaw Y, Simon TA, Cornish A, England BR, et al. Experiences of Patients With Rheumatic Diseases in the United States During Early Days of the COVID-19 Pandemic. *ACR Open Rheumatol.* 2020; 2: 335–343. <https://doi.org/10.1002/acr2.11148> PMID: 32311836
24. Ledford H. Chloroquine hype is derailing the search for coronavirus treatments. *Nature.* 2020; 580: 573. <https://doi.org/10.1038/d41586-020-01165-3> PMID: 32332911
25. Is France's president fueling the hype over an unproven coronavirus treatment? | Science | AAAS. [cited 29 Apr 2021]. Available: <https://www.sciencemag.org/news/2020/04/france-s-president-fueling-hype-over-unproven-coronavirus-treatment>.
26. WHO | Managing Ethical Issues in Infectious Disease Outbreaks. In: WHO [Internet]. World Health Organization; [cited 8 Mar 2021]. Available: <http://www.who.int/ethics/publications/infectious-disease-outbreaks/en/>.
27. Maisonnasse P, Guedj J, Contreras V, Behillil S, Solas C, Marlin R, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature.* 2020; 585: 584–587. <https://doi.org/10.1038/s41586-020-2558-4> PMID: 32698191
28. Roques P, Thiberville S-D, Dupuis-Maguiraga L, Lum F-M, Labadie K, Martinon F, et al. Paradoxical Effect of Chloroquine Treatment in Enhancing Chikungunya Virus Infection. *Viruses.* 2018; 10: E268. <https://doi.org/10.3390/v10050268> PMID: 29772762
29. Kalil AC. Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. *JAMA.* 2020; 323: 1897–1898. <https://doi.org/10.1001/jama.2020.4742> PMID: 32208486
30. Group TRC. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med.* 2020 [cited 24 Mar 2021]. <https://doi.org/10.1056/NEJMoa2021436> PMID: 32678530
31. Schumock GT, Walton SM, Park HY, Nutescu EA, Blackburn JC, Finley JM, et al. Factors that influence prescribing decisions. *Ann Pharmacother.* 2004; 38: 557–562. <https://doi.org/10.1345/aph.1D390> PMID: 14966259
32. Davari M, Khorasani E, Tigabu BM. Factors Influencing Prescribing Decisions of Physicians: A Review. *Ethiop J Health Sci.* 2018; 28: 795–804. <https://doi.org/10.4314/ejhs.v28i6.15> PMID: 30607097

33. Aquino YSJ, Cabrera N. Hydroxychloroquine and COVID-19: critiquing the impact of disease public profile on policy and clinical decision-making. *J Med Ethics*. 2020; 46: 574–578. <https://doi.org/10.1136/medethics-2020-106306> PMID: 32647045
34. Angus DC. Optimizing the Trade-off Between Learning and Doing in a Pandemic. *JAMA*. 2020; 323: 1895–1896. <https://doi.org/10.1001/jama.2020.4984> PMID: 32227198
35. Bull-Otterson L, Gray EB, Budnitz DS, Strosnider HM, Schieber LZ, Courtney J, et al. Hydroxychloroquine and Chloroquine Prescribing Patterns by Provider Specialty Following Initial Reports of Potential Benefit for COVID-19 Treatment—United States, January–June 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69: 1210–1215. <https://doi.org/10.15585/mmwr.mm6935a4> PMID: 32881845
36. Baicus C, Pinte L, Stoichitoiu LE, Badea C. Hydroxychloroquine for prophylaxis of COVID-19 physicians survey: Despite lack of evidence, many would take or give to dear ones, and despite the perceived necessity of an RCT, few would participate. *J Eval Clin Pract*. 2020; 26: 1579–1582. <https://doi.org/10.1111/jep.13484> PMID: 32955801
37. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2017; 2: CD003543. <https://doi.org/10.1002/14651858.CD003543.pub4> PMID: 28178770
38. Kahn SR, Morrison DR, Diendéré G, Piché A, Filion KB, Klil-Drori AJ, et al. Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism. *Cochrane Database Syst Rev*. 2018;2018. <https://doi.org/10.1002/14651858.CD008201.pub3> PMID: 29687454
39. Dagens A, Sigfrid L, Cai E, Lipworth S, Cheng V, Harris E, et al. Scope, quality, and inclusivity of clinical guidelines produced early in the covid-19 pandemic: rapid review. *BMJ*. 2020; 369: m1936. <https://doi.org/10.1136/bmj.m1936> PMID: 32457027
40. Tversky A, Kahneman D. Judgment under Uncertainty: Heuristics and Biases. *Science*. 1974; 185: 1124–1131. <https://doi.org/10.1126/science.185.4157.1124> PMID: 17835457
41. Harrigan JJ, Hubbard RA, Thomas S, Riello RJ, Bange E, Mamtani M, et al. Association Between US Administration Endorsement of Hydroxychloroquine for COVID-19 and Outpatient Prescribing. *J Gen Intern Med*. 2020; 35: 2826–2828. <https://doi.org/10.1007/s11606-020-05938-4> PMID: 32542496
42. Sattui SE, Liew JW, Graef ER, Coler-Reilly A, Berenbaum F, Duarte-García A, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. *Expert Rev Clin Immunol*. 2020; 16: 659–666. <https://doi.org/10.1080/1744666X.2020.1792778> PMID: 32620062
43. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020; 383: 2030–2040. <https://doi.org/10.1056/NEJMoa2022926> PMID: 33031652
44. HCSP. SARS-CoV-2: therapeutic recommendations. Rapp HCSP. Paris: Haut Conseil de la Santé Publique; 2020 Mar. Available: <https://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=801>.
45. Organization WH. Clinical management of COVID-19: interim guidance, 27 May 2020. 2020 [cited 11 Mar 2021]. Available: <https://apps.who.int/iris/handle/10665/332196>.
46. Janda A, Schuetz C, Heeg M, Minden K, Hedrich CM, Kallinich T, et al. [COVID-19: treatment strategies of German-speaking pediatric rheumatologists: Results of an online survey]. *Z Rheumatol*. 2020; 79: 710–717. <https://doi.org/10.1007/s00393-020-00854-8> PMID: 32809050