

1 **Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an**
2 **Open-Label Non-Randomized Clinical Trial: Response to criticisms**

3 Didier Raoult^{1,2}, Matthieu Million^{1,2}, Jean-Christophe Lagier^{1,2}, Philippe Colson^{1,2}, Philippe
4 Parola^{1,3}, Jean-Marc Rolain^{1,2}, Philippe Gautret^{1,3}

5 **Affiliations :**

6 ¹ IHU-Méditerranée Infection, Marseille, France

7 ² Aix Marseille University, IRD, AP-HM, MEPHI, Marseille, France

8 ³ Aix Marseille University, IRD, AP-HM, SSA, VITROME, Marseille, France

9 **Corresponding author:** Didier Raoult, IHU - Méditerranée Infection, 19-21 boulevard Jean
10 Moulin, 13005 Marseille, France. Tel.: +33 413 732 401, Fax: +33 413 732 402; email:
11 didier.raoult@gmail.com

12 **Key words:** SARS-CoV-2; COVID-19; hydroxychloroquine; azithromycin

13 We thank the authors for comments provided for our article (1-3), but we would like to clarify
14 key points for the story of this manuscript (4) that are critical in the context of COVID-19
15 outbreak and for the perspective of this work. When COVID-19 starts around the world the
16 Editor-In-Chief of the Journal International Journal of Antimicrobial Agents (JM. Rolain)
17 asked colleagues (D. Raoult, PR. Hsueh, and S. Stefani) to launch a special issue in the
18 journal to create a real-time rapid debate around this emerging disease with special regards to
19 therapeutic options (5). Our preliminary paper (4) in this way was relatively trivial i.e
20 reported, in an emergency situation, a comparative analysis between a small group treated
21 with hydroxychloroquine and another small group not treated with hydroxychloroquine
22 showing a significant decrease of viral shedding after 6 days of therapy.

23 Surprisingly, despite the very small size of the group, the addition of azithromycin
24 made a difference on the endpoint we chose, which is the disappearance of the viral load in
25 the pharynx that is the only data that can be analyzed on a small group (6). Indeed, neither
26 mortality, nor the passage in intensive care unit, nor the duration of the treatment can be
27 evaluated on such a small group (6). This preliminary information was essential in our
28 opinion especially as it confirmed the preliminary *in vitro* and *in vivo* results against SARS-
29 CoV-2 announced by the Chinese (7-9), also confirming previous *in vitro* reports on the anti-
30 SARS-CoV-1 coronavirus activity dating back to 2004 (10-13). This preliminary report paved
31 the way for work testing its reproducibility.

32 On the therapeutic level, the hydroxychloroquine + azithromycin combination was
33 found to be the most effective (4) consistent with *in vitro* synergistic antiviral activity
34 reported in our laboratory (14,15). Azithromycin had already, contrary to what one of the
35 authors says, been tested effectively on Zika (16, 17), so we knew that it had an antiviral
36 action. With regard to our seminal paper on *in vivo* anti-SARS-CoV-2 activity of
37 hydroxychloroquine (4), we were subjected to unprecedented violence. I (DR) was asked to

38 confess that I had a relationship and a conflict of interest with Sanofi, which is laughable
39 when you use generics and you have had no relationship with the pharmaceutical industry at
40 all at IHU (our center) for 5 years. The second thing is that I (DR) was harassed to give all the
41 evidence to show that this was done after the agreement of our government, the evaluation by
42 the Committee for the Protection of Individuals, and that it was done in all regularity
43 (validated by ANSM, the French FDA, available online in the EU Clinical Trial Register Page,
44 EudraCT number: 2020-000890-25). Subsequently, we were threatened for retraction of this
45 article, with no justification other than the opinion of people who were fiercely hostile to the
46 use of hydroxychloroquine. It should be noted that this paper is now by far the most cited
47 paper in the literature on the treatment of COVID-19, exceeding 2,500 citations in Google
48 Scholar.

49 As a result of this paper, half of the world's population lives in countries where
50 hydroxychloroquine with or without azithromycin is largely prescribed against COVID-19,
51 this currently concerns more than 4.5 billion people (18). On the other hand, methodological
52 problems and problems of scientific misconduct with non-declaration of conflict of interest
53 have multiplied for therapeutics in the best journals which ended up with the retraction of a
54 paper (19).

55 Over the past few decades, randomized controlled trials (RCTs) have been considered
56 the ultimate in defining the best treatment for a disease, especially in large international multi-
57 center studies largely funded by pharmaceutical companies. This is not true because there are
58 no significant differences in effect estimates between observational studies and RCTs,
59 regardless of the specific design of the observational studies, heterogeneity or inclusion of
60 studies of pharmacological interventions as demonstrated by a Cochrane review that analyzed
61 1583 meta-analyses covering 228 different medical conditions (20). RCTs introduce several
62 biases (21), including that the physicians and patients included in these trials are not the same

63 as those included in observational studies (selection bias). Furthermore, the fact that RCTs on
64 the same disease produce heterogeneous results with different directions of the effect shows
65 that these approaches are not accurate (22) and does not prevent the effect of confounding
66 factors. This inaccuracy has also been illustrated by the fact that the range for point estimate
67 was wider for randomized, controlled trials than for observational studies in a meta-analysis
68 of 99 reports on 5 different medical conditions from 5 major medical journals (Annals of
69 internal medicine, BMJ, JAMA, the Lancet, and the New England Journal of Medicine) (23).

70 The limited role of RCTs in clinical practice is also confirmed by the fact that the
71 majority (>80%) of infectious disease recommendations are not based on any placebo-
72 controlled RCT. For example, the recommendations in the Infectious Diseases Society of
73 America (IDSA) clinical practice guidelines are primarily based on evidence from non-
74 randomized studies or expert opinion. Evidence based on at least one RCT makes up only
75 16% of the recommendations (24). This is also the case, for example, for quinine for malaria,
76 penicillin, treatment of syphilis, treatment of typhoid, Q fever, Whipple's disease, and most
77 vaccines, including rabies vaccine.

78 Beyond RCTs, big data studies were presented as a new reference. Here, we report an
79 update of a meta-analysis (25) that highlights the Simpson's paradox (26): Big data studies,
80 which "pool" raw data from very different groups, produce very heterogeneous and
81 inconsistent results, whereas clinical studies, conducted by physicians who see patients, have
82 consistent results. Overall, all of this suggests that well-conducted observational studies
83 conducted by physicians who see patients and who know the disease are the best approach to
84 control confounding factors and to define optimal patient management, particularly in an
85 acute fatal pandemic disease such as COVID19 (21,23).

86 Finally, we have recently carried out a meta-analysis of all the work done on
87 hydroxychloroquine (25) that is upgraded in this response. Here, we specifically focused on

88 mortality and viral shedding persistence, including two new randomized controlled trial
89 reporting a favorable effect on viral shedding (27,28) (Figure 1). Importantly, while the
90 conflict has been particularly violent in France and the United States, 5 studies from both
91 these countries have shown that hydroxychloroquine reduces rate of hospitalization, length of
92 hospitalization, mortality, and viral shedding in 4,642 (29), 3,737 (30), 2,820 (31), 2,541 (32)
93 and 518 (33) patients. The methods are detailed in the supplementary data.

94 This new meta-analysis (Figure 1) included, for the mortality outcome, 48,655 patients
95 (including 29,153 treated by a chloroquine derivative) from 31 studies in 11 countries
96 (Andorra (34), Belgium (35), Brazil (36), China (37), Egypt (38), France (29,30,39-43), Italy
97 (44-47), Iran (48), Saudi Arabia (49), Spain (50-52), USA (31-33,53-57), and two
98 multinational teams (58,59). Studies assessing the death outcome but excluded from the
99 present analysis and reasons for exclusion are detailed in Supplementary Table 1. Data
100 extracted from the included studies for the mortality outcome are reported in Supplementary
101 Table 2. A two-fold decrease of the risk of death was confirmed in clinical studies (number of
102 comparisons (n) = 23, odds ratio 0.56, 95% confidence interval (95%CI) 0.48 – 0.65, p =
103 7.47×10^{-13}) and among big data studies (n = 14, OR = 0.89, 95%CI 0.81 – 0.98, p = 0.022 –
104 Figure 1A). Heterogeneity was significant between clinical and big data studies (Q-value
105 39.8, p = 2.8×10^{-10}). Effect size was consistent among clinical studies ($I^2 = 29\%$, p = 0.09) but
106 not among big data studies ($I^2 = 78\%$, p = 7.1×10^{-8}). Indeed, for instance, a big data study (31)
107 recently reported a very significant two-fold decrease in mortality in 2,820 patients from the 8
108 hospitals of the Mount Sinai Health System (New York, USA). This result contrasts with
109 other big data studies (29,53,57). Despite substantial heterogeneity, a significant summary
110 effect was observed when including all comparisons from all included studies (n = 37, OR
111 0.78, 95%CI 0.72 - 0.85, p = 1.1×10^{-8}). Exclusion of the study from our center (30) did not
112 modify neither the overall effect (n = 36, OR = 0.76, 95%CI 0.69 – 0.84, p = 6.0×10^{-8}) nor the

113 two-fold decrease in the risk of death among 18 clinical studies from other centers (n = 22,
114 OR 0.55, 95%CI 0.46 - 0.65, p = 2.0x10⁻¹¹).

115 Looking at persistent viral shedding, a total of 5,204 patients (3,765 treated by a
116 chloroquine derivative) from 12 studies from only 6 countries were included (5 from China
117 (27,60-63), 2 from France (30,42), 1 from Pakistan (28), 1 from Saudi Arabia (64), 2 from
118 South Korea (65,66) and 1 from Taiwan (67). Studies assessing the viral shedding outcome
119 but excluded from the present analysis and reasons for exclusion are detailed in
120 Supplementary Table 3. Data extracted from the included studies for the viral shedding
121 outcome are reported in Supplementary Table 4. Overall, a substantial heterogeneity was
122 found among all study (I² = 78%), and this heterogeneity remained unchanged after excluding
123 the only one found as a big data study associated with unfavorable outcome (66). Meta-
124 analysis of clinical studies evidenced a significant two-fold decrease of the risk of viral
125 persistence (13 comparisons, OR 0.50, 95%CI 0.32 – 0.79, p = 0.003, Figure 1B). Exclusion
126 of our study (30) did not change the effect size (n = 12, OR = 0.48, 95% CI 0.26 – 0.87).
127 Strikingly, none of the studies from USA assessed the virus persistence (68).

128 This new meta-analysis shows that, apart from the unverifiable work that did not
129 assess virological outcome and carried out by people who had conflicts of interest with the
130 pharmaceutical industry (69), the body of publications shows that hydroxychloroquine
131 therapy is significantly and reproducibly correlated with a two-fold decrease in both mortality
132 and viral shedding.

133 In practice, our seminal work (4) has benefited from a massive diffusion despite a
134 profusion of papers that have not been verified but accepted each time they had a negative
135 position towards hydroxychloroquine (6,68). However, the facts being stubborn, the
136 accumulation of publications showing that hydroxychloroquine is effective following our
137 paper leaves no doubt that this preliminary study did indeed paved the way for a therapeutic

138 strategy that is now being generalized throughout the world, and whose favorable results have
139 been replicated several times. In addition, a group of American and Italian experts recently
140 recommended the use of hydroxychloroquine and azithromycin in COVID-19 outpatients at
141 the early stage of the infection (70).

142 **Acknowledgements**

143 We thank Yanis ROUSSEL for his contribution to the preparation of this response.

144 **Funding**

145 None

146 **Ethical approval**

147 Nor required

148 **Declaration of competing interest**

149 The authors declare no competing interests. Funding sources had no role in the design and
150 conduct of the study; collection, management, analysis, and interpretation of the data; and
151 preparation, review, or approval of the manuscript. Our Marseille group used widely available
152 generic drugs distributed by many pharmaceutical companies.

153 **Authors' contributions statement:**

154 Writing – original draft: MM, PG & DR

155 Writing – review & editing: JCL, PC, PP, JMR & DR

156 Conceptualization: DR

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398 **Figure 1. Meta-analysis on chloroquine derivatives against COVID-19**

399 A. Mortality, B. Viral shedding. CI: confidence interval, HCQ: hydroxychloroquine, CQ:
400 chloroquine, AZ: Azithromycin, RCT: randomized controlled trial. This meta-analysis was
401 performed with a random-effects model using Comprehensive Meta-Analysis v3 (Biostat,
402 Englewood, NJ, USA). Randomized controlled trials are labeled “RCT” (highlighted in
403 yellow) and studies whose authors reported conflicts of interests are written in red. *In this
404 study, 226 patients were included but only 40 matched patients were included in the
405 multivariate statistical analysis.