SUPPLEMENTARY DATA

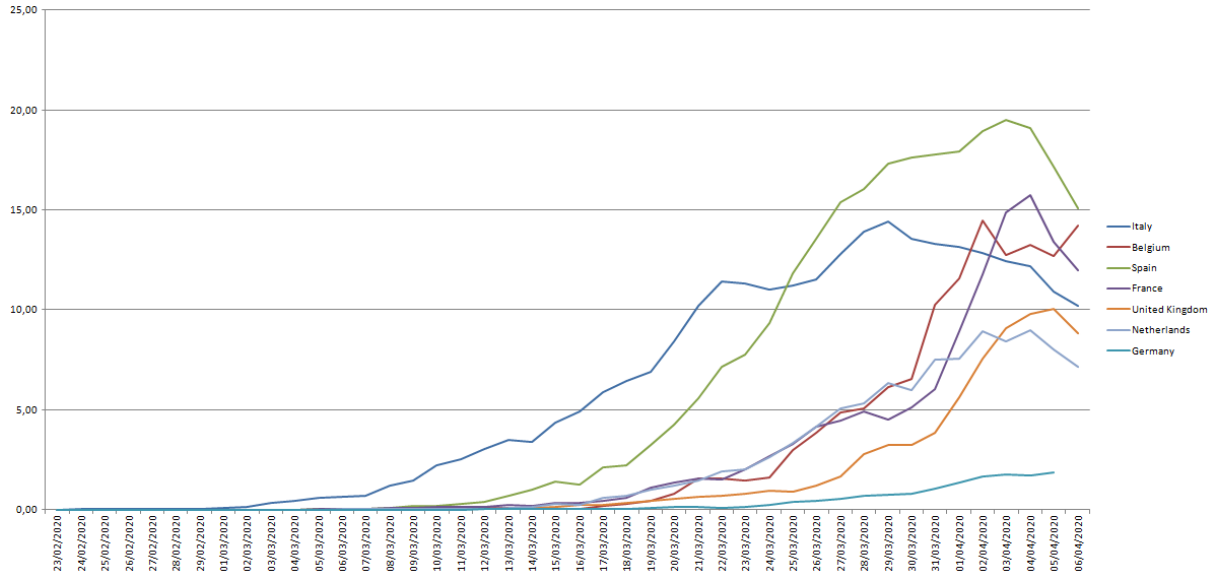
SUPPLEMENTARY MATERIAL

Specific inclusion protocol and follow-up for *torsade de pointes* risk in patients treated with a combination of hydroxychloroquine and azithromycin.

Any drug with the potential to prolong the QT interval and non-vital potassium-depleting drugs (diuretics prescribed for high blood pressure) were systematically stopped. When potassium-depleting drugs could not be stopped or in case of documented hypokalaemia at admission, potassium supplementation was provided and hydroxychloroquine was administered only when potassium level was normalized. Close ionogram monitoring was performed in patient with low serum potassium levels at baseline. An electrocardiogram was routinely performed 48 hours after the start of treatment. Treatment with hydroxychloroquine was discontinued when the corrected QT interval (QTc, Bazett's formula) was > 500ms and the risk-benefit ratio of HCQ+AZ treatment was estimated by the infectologist and agreed with the cardiologist, at between 460 and 500ms. The indications for this control ECG were restricted after an initial workup in 848 ECG from 424 patients (at day 0 and day 2 for each patient) showing that all contraindicative repolarization abnormalities had been detected on the first ECG [1].

SUPPLEMENTARY FIGURES

Supplementary Figure S1. Phylogenetic tree of SARS-COV-2 genomes including isolates from six persistent viral shedders and nine treatment-responding patients (green branches). *** = poor virological outcome**,** and ¶ = poor clinical outcome. Phylogenetic reconstruction was performed using NEXSTRAIN (https://nextstrain.org/) and GISAID (Global Initiative; https://www.gisaid.org/) with acknowledgments [2].



Supplementary Figure S2. Daily mortality for one million inhabitants, mitigated on three days.

SUPPLEMENTARY TABLES

Supplementary Table S1. Reasons for exclusion of 350 patients from the study

94 previously published	[3,4]
33 with cardiac contraindication	11 non specified 10 prolonged QTc 3 Brugada syndrome 1 myocarditis history 1 left ventricular hypertrophy 1 severe ischemic cardiopathy 1 left bundle branch block 1 right bundle branch block 1 atrio-ventricular block 1 supraventricular tachycardia 1 ECG abnormities suggesting underlying cardiac ischemic disease 1 unspecified arrhythmia
28 considered cured by the physician based on clinical feature	
21 refusal of hydroxychloroquine or azithromycin treatment	
15 with potential risk for drug interactions with hydroxychloroquine or azithromycin treatment	Cardiac drugs 3 flecainide 2 amiodarone 1 bisoprolol 1 nicardipine Neuropsychiatric drugs 2 escitalopram 1 levetiracetam 1 cyamemazine 1 venlafaxine 1 lamotrigine 1 valproate 1 lithium Others 1 cabergoline 1 dolutegravir/rilpivirine
10 hypokaliemia	
6 children < 15 years	
6 ophtalmologic contraindication to hydroxychloroquine treatment	3 retinopathy 2 glaucoma 1 accomodation disorder
4 known allergy to hydroxychloroquine or azithromycin treatment	
2 breastfeeding	
2 gastrointestinal intolerance to hydroxychloroquine or azithromycin treatment	
2 swallowing disorders	
1 insomnia	
61 under hydroxychloroquine only before the publication of the first study [3] that led to the systematic use of dual therapy with azithromycin on March 20, 2020.	
66 unspecified	

The reasons mentioned here are those retained by physicians who have seen the patients and do not necessarily correspond to formal contraindications. Several reasons may coexist in a same patient.

Supplementary Table S2. Clinical data of eight patients who died from COVID19 infection out of 1,061 treated with hydroxychloroquine or azithromycin for at least three days. Day 0 between March 3rd and March 31, 2020; Follow up regarding fatal issue : April 18th, 2020

Age, median (min-max)	79 (74-95)
Chronic condition	
Hypertension, N (%)	6 (75%)
Cancer, N (%)	1 (12.5%)
NEWS score, mean (min-max)	7.75 (5-11)
Time between symptoms and hospitalization, mean (min-max)	5.6 days (2-14)
Time between hospitalization and death, mean (min-max)	16 days (6-26)
Day 2-hydroxychloroquine blood level (µg/mL), mean (min-max)	0.162 (0.071-0.338)

Supplementary Table S3. Cumulative death and mortality per million population by COVID-19 on 2020, 6th April.

	Death (N)	Mortality per million population
France	6,494	96.8
Marseille city*	51	59.1
Bouches-du-Rhône	121	59.5
Rhône	233	124.2
Europe	53,039	71.5
Spain	13,055	278.1
Italy	16,523	273.7
Belgium	1,632	142.4
Netherlands	1,867	105.2
United Kingdom	5,373	80.6
Germany	1,434	17.2
China	3,338	2.4
Korea	192	3.7
USA	10,989	33.6

* Patients living in Marseille city and diagnosed at AP-HM by IHU laboratory

Supplementary Table S4. Mortality and mean age of patients with SARS-CoV-2 infections and other respiratory virus infections from 2017, 1st December to 2020, 6th April at AP-HM

	Number of patients	Number of deaths	%	Age of dead patients		
				median	mean	sd
SARS-CoV-2	4940	63	1.0	**82**	**79.6**[a]	13.6
Influenza A virus	4735	72	1.4	**73.5**	**69.8**[b]	21.0
Influenza B virus	2087	20	1.0	**84**	**83.5**[c]	9.7
Respiratory syncytial virus	2993	37	1.2	**82**	**76.0**[d]	24.5

[a] vs [b], p= 0.0021 (Wilcoxon test),
[a] vs [c], not significant
[a] vs [d], not significant
[b] vs [c], p-value = 0.0036
[b] vs [d], p-value = 0.011
[c] vs [d], not significant
Sd, standard deviation

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[2] Hadfield J, Megill C, Bell SM, Huddleston J, Potter B, Callender C, et al. Nextstrain: real-time tracking of pathogen evolution. Bioinformatics 2018;34:4121-4123.

[3] 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;105949. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print]

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