- 1 <u>Title</u>: Evaluation of strategies to fight COVID-19: The French paradigm
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26 <u>Abstract</u>

27 Background:

The management of COVID-19 has been highly discrepant across the world. In France, no mass screening has been performed, containment has been implemented, and no therapy has been officially approved. Our institute chose to screen anyone who came forward, and a combination therapy of hydroxychloroquine and azithromycin was offered to positive patients. To evaluate our data in a global context, we collected mortality data and the age distribution of the deceased in France and other European countries, as well as specifically in the cities of Paris and Marseille, and compared them.

35 Materials and methods:

Data on mortality related to COVID-19 and the associated age distribution were collected from government institutions in various European countries. In France, data were obtained from INSEE and Santé Publique France. All-cause mortality was also examined in order to study potential excess mortality using EuroMOMO. The Marseille data came from the epidemiological surveillance system set up by our institution covering 4 university hospitals in Marseille.

42 Findings:

43 France is one of the European countries most impacted by COVID-19, behind Belgium, Spain, 44 the United Kingdom and Italy. Its proportion of deaths in people under 60 years of age is higher (6.5%) than that of Italy (4.6%) or Spain (4.7%). Excess mortality was also observed, 45 46 with approximately 5% more deaths than during the corresponding dates in 2018 and 2019. Ile-de-France and the Grand Est are the two French regions with the highest mortality (647 47 and 592 deaths per million inhabitants vs. 181 in the Southern region, where our institute is 48 located). However, the proportion of deaths in the under-60 age group was considerable in 49 50 Ile-de-France (9.9% vs. 4.5% in the Southern region). By estimating mortality based on 51 seroprevalence, we observed an excess of deaths in Ile-de-France and the Grand Est, while the 52 expected mortality in the Bouches-du-Rhône (a department of the Southern region) was lower 53 than expected. Significantly higher numbers of patients hospitalized, in intensive care and 54 deceased in Paris than in Marseille.

55 **Discussion:**

France's strategy of privileging randomized clinical trials of severe patients to the detriment of
patient management, i.e., from screening to diagnosis, including biological assessment and
clinical examination, probably explains the high mortality associated with COVID-19.

60 Introduction

61 In December 2019, a novel coronavirus known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) emerged and spread from Hubei Province, China, to the rest of the 62 world in a few months. The disease (COVID-19) did not spare any continent and was 63 64 declared a pandemic by the WHO on 11 March 2020. As of October 5, 2020, 35,220,166 cases of COVID-19 and 1,037,604 deaths related to this disease had been reported worldwide 65 66 [1]. The epidemic seemed to be diminishing or even stopping in Western European countries 67 in June, as has been observed in Asia, but an upsurge in the number of cases was observed in early July where borders were reopened. 68

The management of COVID-19 has been subject to considerable divergences around 69 70 the world. These divergences have concerned containment measures, the systematization of virus detection tests, isolation and therapeutic strategies. The same is true within France. 71 72 Indeed, to limit the spread of the virus, the French government initially decided to close 73 schools and universities [2] as well as all cultural facilities, such as theatres and museums, 74 and cancelled large gatherings of people [3]. A total lockdown was finally decreed on 17 March 2020 with the objective of stopping the chain of transmission [4]. However, unlike in 75 76 Iceland or South Korea, no mass screening was then carried out systematically on a national 77 scale in the early stage of this pandemic, which would have made it possible to quickly obtain 78 information on the incidence of the disease and thus put in place public health measures better 79 adapted to the particularities of the spread of the virus in our territory [4-6]. Only "individuals 80 with clinical signs of acute respiratory infection with documented or subjective fever who have travelled to or stayed in a high-risk exposure area within 14 days prior to the date of 81 onset of clinical signs, or individuals who have had close contacts with a confirmed COVID-82 19 case or any person showing signs of pneumonia or acute respiratory distress" were 83 screened in March 2020 [7]. These positive patients were quarantined for 14 days. Finally, 84

mass screening was proposed on May 11, 2020, when lockdown was lifted and bordersreopened.

In Marseille, organized mass screening was carried out beginning January 27, 2020, comparable to what was implemented in Iceland, and hydroxychloroquine/azithromycin combined therapy (HCQ+AZ) was proposed in our institute for most COVID-19 patients [8]. In Paris and the Ile-de-France region, early treatment was not proposed, nor was any therapy that was not officially approved until the end of May and the lockdown [9].

We were interested in comparing the epidemic level and lethality under such different 92 conditions to evaluate strategies involving only social measures versus both social and 93 94 medical measures. We collected available data on testing strategies, therapeutic options and 95 lockdowns in different countries and in the cities of Paris and Marseille, and we compared the mortality. We paid special attention to the percentage mortality by age, which appeared to us 96 97 to be an important marker. Indeed, mortality in people over 80 years of age is usually high in the winter and summer periods in temperate countries due to the circulation of common 98 99 respiratory viruses. It is possible that mortality in people under 60 years of age can serve as a marker of the effectiveness of therapeutic management in a given situation. 100

101 Materials and methods

102 *COVID-related mortality in France and other European countries*

103 The mortality associated with COVID-19 in France and different European countries was collected from the Center for Systems Science and Engineering (CSSE) at Johns Hopkins 104 105 University [1] as of June 2, 2020. To correct the biases linked to the size of the countries, we calculated the mortality rate per million inhabitants. The case fatality rate (CFR, the ratio of 106 107 the number of deaths to the number of confirmed cases, i.e., the lethality rate) was obtained from the aggregator site Our World in Data as of June 2, 2020. The age distribution of 108 109 individuals who died from COVID-19, when available, was collected for several countries. 110 Data for the United Kingdom were collected from the National Health Service (NHS) 111 (https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-daily-deaths/) as of 112 June 2; those for Italy were collected via Epicentro, Istituto Superiore di Sanità 113 (https://www.epicentro.iss.it/) as of 1 June; those for Spain were collected via El Centro de Epidemiologia (CNE) (https://cnecovid.isciii.es/) as of May 29; and those for Germany were 114 115 collected via INED (https://dc-covid.site.ined.fr/en/data/germany/) by June 2. The proportion of deaths among people under 60 years of age was calculated. The mortality aboard 3 ships, 116 117 namely, the Diamond Princess, the Roosevelt and the Charles de Gaulle, has also been 118 documented in the literature [10-12].

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Excess all-cause mortality in France and other European countries

All-cause mortality in France and at the regional level according to the decedents' place of residence between January 1 and August 31 for 3 years (2018, 2019 and 2020) was collected from the INSEE database [13] to assess potential excess mortality. Excess mortality in Paris and Marseille was also studied using the same database. The excess mortality by country and by age group (0-14, 15-44 and 45-65 years) was retrieved from the EuroMOMO website (https://www.euromomo.eu/graphs-and-maps), which collects all-cause mortality data from several European partner countries such as France, the United Kingdom, Italy and Spain. The excess mortality was estimated using the z-score, which allows comparisons of mortality between the different countries and the different time periods studied [14].

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French departmental and regional data on COVID-19

Daily hospital data related to COVID-19 by French region and department were obtained 133 134 from Santé Publique France, a public health institute in France [15]. These data were 135 available only from March 19 onward, and our study period was therefore limited to March 136 19 to June 2, 2020. To correct for biases related to population size in each region and 137 department, we calculated the mortality rate in France per million inhabitants. The size of each regional population was retrieved from the Institut National d'Études Démographiques 138 139 (INED) database [16]. The population of each department was collected from the INSEE 140 database.

141 Deaths associated with COVID-19 by age group according to region were retrieved from142 GEODES, the French Public Health mapping observatory, over the same study period [17].

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Seroprevalences in French regions and probability of mortality

Adjusted estimates of seroprevalences in Ile-de-France, in the Grand Est, and in New Aquitaine were collected in an article preprinted on MedRxiv in September 2020 [18]. The seroprevalence in the Bouches-du-Rhône is based on data from the Blood Establishment and is still unpublished. The overall probability of death among the infected cases was collected in the study of Salje et al., 2020, and equals 0.5% [19]. 150

151 *Marseille data*

152 Local data for the city of Marseille were obtained by using the epidemiological surveillance system from our institute that collects information on patients hospitalized at Assistance 153 154 Publique – Hôpitaux de Marseille (AP-HM), which comprises four public university hospitals [20,21]. This system is based on the results from the clinical microbiology laboratory of the 155 156 IHU Méditerranée Infection, and includes microbiological results (sample type, sample date, 157 requesting unit) and anonymous patient information (age, sex, home postal code, date of 158 admission), stored in a data warehouse using MariaDB. COVID-19-associated mortality data 159 were obtained from the Department of Medical Information (DMI) of AP-HM.

160 The size of the Marseille population was also obtained from the INSEE database [22].

161 These data were collected from January 27 to May 31, 2020.

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163 *Statistical analysis*

164 The statistical analyses performed OpenEpi were with software (https://www.openepi.com/TwobyTwo/TwobyTwo.htm?fbclid=IwAR0NjbfgL6G7d77LiFSY 165 166 TzdJAbK3YIPaYi2ZDFEeCnhFqbHFuMfibs1jaWI). A chi-square test or mid-P test was used 167 to compare groups, depending on the variables. The graphs were created using the software R [23] with the ggplot2 package [24] and using Excel. 168

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170 <u>Results</u>

Overall analysis and positioning of France in relation to other European countries
France, with 28,836 deaths, is one of the countries most impacted by COVID-19 in Europe.
Its mortality rate is 441.8 deaths per million inhabitants, placing it behind Belgium (825.4),
Spain (580.2), the United Kingdom (576.6) and Italy (553.6). However, its case fatality rate

(CFR) was 20%, the highest in Europe. France is also one of the countries where the 175 176 proportion of individuals under 60 years of age was especially high (6.5%, N = 1.201), exceeding the rates in Italy (4.6%, N = 1.487), Spain (4.7%, N = 969) and Germany (4.5%, N 177 = 378) (Figure 1). The United Kingdom reached 8.6% (N = 2.336). There were no deaths on 178 the French warship Charles de Gaulle. One death (2.3%) of a 41-year-old man was recorded 179 180 on the USS Theodore Roosevelt. On the Diamond Princess, a cruise ship, the majority of 181 those who died were over 80 years of age (7.4%). Overall, Belgium, France, Italy, the 182 Netherlands, Spain, Sweden and the United Kingdom had excess mortality at least 10 standard deviations above the mean. For the 45-65 age group, this excess mortality was 183 184 highest for England (z-score of 25.9), followed by Spain (16.5) and France (8.8).

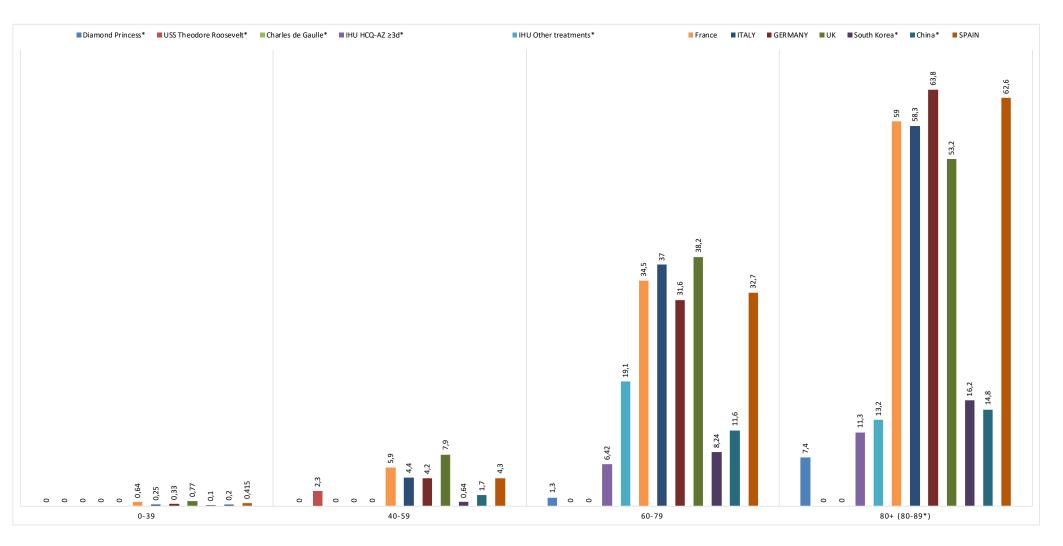


Figure 1 – Mortality rate by age group on 3 ships (the Diamond Princess, the USS Theodore Roosevelt and the Charles de Gaulle) and in France, Italy, Germany, the United Kingdom (UK), South Korea, China, Spain and our institute following treatment.

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Comparison of excess all-cause mortality

191 In France overall, 430,254 deaths due to all causes were observed between January 1st, 2020, and August 31, 2020. This corresponds to an increase in the number of deaths by 4.6% and 192 193 5.0% compared to 2018 and 2019, respectively, for the corresponding periods of time (Table 1). The excess mortality was high in dependent elderly residents in retirement homes and at 194 195 home but was not noted among hospitalized patients. Ile-de-France had the highest excess all-196 cause mortality (+22%) nationwide, while a decrease was observed in New Aquitaine (Table 197 1). In Ile-de-France, the highest excess mortality was observed in residential facilities for 198 elderly dependents and in hospices (+48% compared to 2018 and +55.3% compared to 2019). 199 Excess mortality at home was approximately 28% in Ile-de-France, 14% in Grand Est, 6% in Sud and 2% in New Aquitaine. However, hospital mortality has decreased in Sud 200 201 (approximately -6%) and New Aquitaine (approximately -4%), while it has increased in Ilede-France and Grand-Est by 15% and 6%, respectively. Regardless of the location of death, 202 203 April had the highest excess mortality, with an increase of 32.7% over 2018 and 36.1% over 2019. A lower excess mortality of 17% (compared to 2019) was visible as early as March, 204 205 particularly for Grand-Est. There was no significant increase or decrease in the other months 206 studied (Supplementary data S1, S2, S3, S4).

8 Table 1 – Excess mortality in 2020 compared to 2018/2019 from January to August in France, including 4 regions. The data were collected from the INSEE

9 database.

y database.						2020 vs 2018					
		Sud	Ile-de-France			Grand-Est		New-Aquitaine		France	
	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	
Deaths from all causes	34,176	321 (0.9%)	50,386	10,966 (21.8%)	36,194	4,150 (11.5%)	44,017	-1,175 (-2.7%)	411,271	18,983 (4.6%)	
Deaths from all causes in public or private hospitals	17,695	-1,039 (-5.9%)	30,790	4,622 (15.0%)	21,099	1,017 (4.8%)	22,485	-1,063 (-4.7%)	219,669	- 1,104 (-0.5%)	
Deaths from all causes in hospice or among dependent elderly residents in retirement homes	3,981	190 (4.8%)	5,196	2,493 (48,0%)	5,078	1,463 (28.8%)	6,859	-3 (0.0%)	51,634	5,908 (11.4%)	
Deaths from all causes at home	9,721	597 (6.1%)	10,674	3,119 (29.2%)	7,979	1,083 (13.6%)	10,931	100 (0.9%)	98,624	7,060 (7.2%)	

	2020 vs 2019									
		Sud	Ile-de-France		Grand-Est		New-Aquitaine		France	
	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)
Deaths from all causes	34,267	230 (0.7%)	50,556	10,796 (21.4%)	35,654	4,690 (13.2%)	43,791	-949 (-2.2%)	409,835	20,419 (5.0%)
Deaths from all causes in public or private hospital	17,784	-1,128 (-6.3%)	31,045	4,367 (14.1%)	20,534	1,582 (7.7%)	22,266	-844 (-3.8%)	217,409	1,156 (0.5%)
Deaths from all causes in hospice or among dependent elderly residents in retirement homes	4,135	36 (0.9%)	4,952	2,737 (55.3%)	4,862	1,679 (34.5%)	6,473	383 (5.9%)	49,578	7,964 (16.1%)
Deaths from all causes at home	9,659	659 (6.8%)	10,843	2,950 (27.2%)	7,976	1,086 (13.6%)	10,686	345 (3.2%)	96,429	9,255 (9.6%)

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Mortality rates associated with COVID-19 in France

211 Three groups seemed to emerge according to mortality rates. Grand-Est and Ile-de-France 212 were the two regions most impacted by COVID-19, with 647 and 592 deaths per million inhabitants, respectively (Figure 2). However, this rate was significantly higher in Grand-Est 213 than in Ile-de-France (p-value <0.001). Haut-Rhin, a department in the Grand-Est region, had 214 the highest mortality rate, with 1,095 deaths per million inhabitants. Within the Ile-de-France 215 216 region, Paris was the most impacted department, with 798.9 COVID-19-related deaths per 217 million inhabitants. Bourgogne-Franche-Comté and Hauts-de-France (regions bordering the 218 two previous regions) had lower incidence rates, as did the island of Corsica, with 367, 299 219 and 168 deaths per million inhabitants, respectively (p-value <0.001). The other regions, 220 including the Sud region (formerly known as the Provence-Alpes-Côte d'Azur region) (181 221 deaths per million inhabitants) and New-Aquitaine (70 deaths per million inhabitants), had 222 mortality rates almost 3 times lower than that of the Grand-Est region. The Bouches-du-Rhône, a department in the Sud region where our institute is located, had a mortality rate of 223 224 263 deaths million inhabitants. per

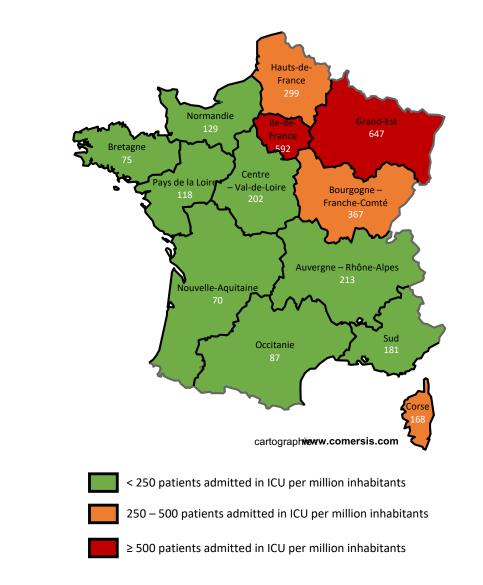


Figure 2 – Regional distribution of COVID-19 mortality per million inhabitants. Green indicates regions that were less impacted by COVID-19, orange
 indicates regions that were moderately impacted by COVID-19 and red indicates regions that were strongly impacted by COVID-19.

229 *Mortality associated with COVID-19 in people under 60 years of age*

COVID-19 killed mainly patients over 80 years of age. The 80-89 age group appeared to bethe most impacted age group nationally, regionally and locally (Supplementary Table S5).

232 Mortality rates in patients under 60 years of age varied according to region (Figure 3). This percentage reached 9.9% (N = 701) in the Ile-De-France region, which was significantly 233 higher than that observed in the Sud region (4.5%, p-value = 0.0000003), in the Grand-Est 234 region (4.4%, p-value = <0.0000001), in the Auvergne-Rhône-Alpes region (3.7%, p-value = 235 236 <0.0000001) and in France overall (6.5%, p-value = <0.00000001). No significant difference was observed regarding mortality in patients under 60 years among the Sud region (4.5%), the 237 238 Auvergne-Rhône-Alpes region (3.7%) and the Grand-Est region (4.4%) (Supplementary 239 Table S6).

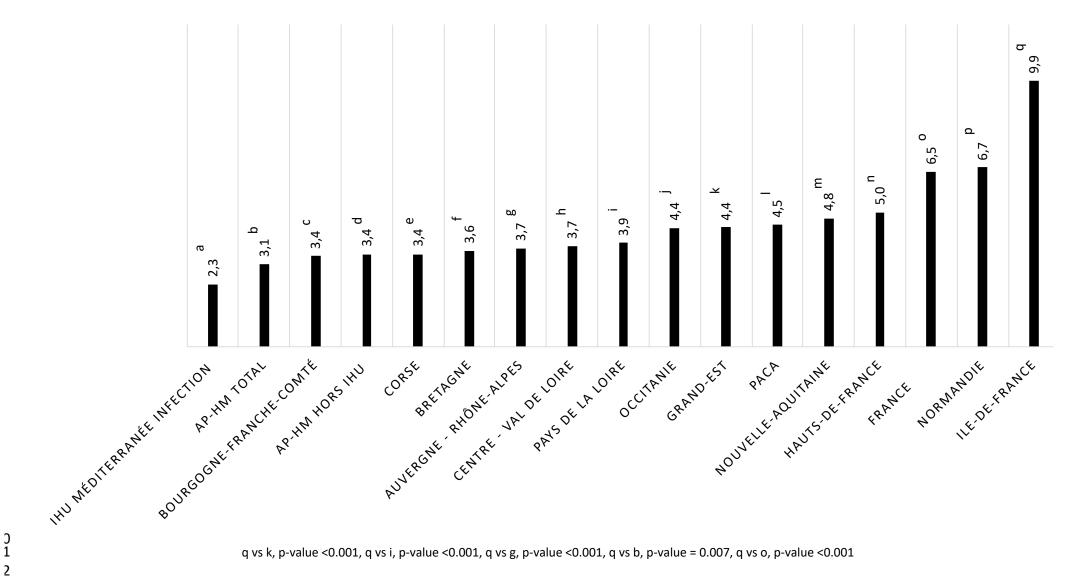


Figure 3 – Comparison of mortality associated with COVID-19 in patients under 60 years of age at IHU Méditerranée Infection, at AP-HM, in French regions
 and in France overall.

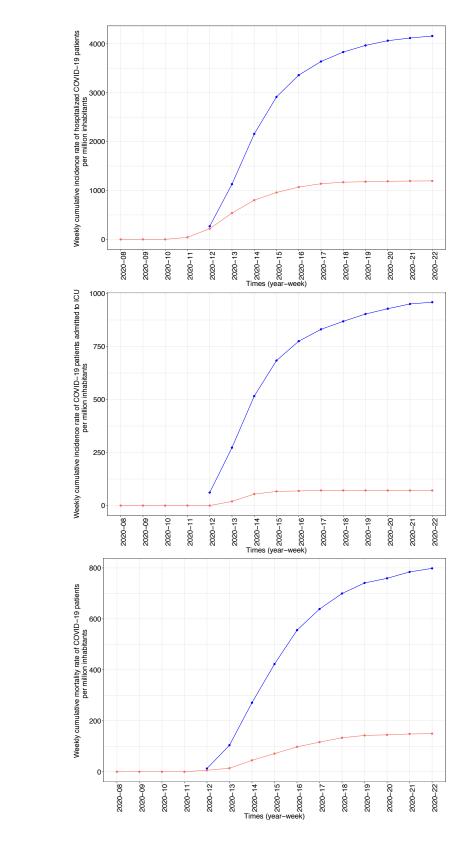
245	Mortality	estimation according	g to the prevalence of an	tibodies tested afte	r the first
246	outbreak				
247	In the Ile-de-Fran	ce region as well as	in the Grand-Est region,	an excess of deaths	s could be
248	observed compare	ed to what was expect	ted (592 deaths per million	n inhabitants instead	l of 500 in
249	the Ile-de-France	region and 647 deat	hs per million inhabitants	instead of 450 in t	he Grand-
250	Est region) (Table	e 2). Conversely, the	e Sud and New Aquitaine	regions had lower	mortality
251	per	million	inhabitants	than	expected.

2 Table 2 – Mortality estimation according to the prevalence of antibodies after a delay.

Region	Population size (inhabitan ts)	Seroprevalence (%)	Number of estimated COVID-19 cases on the basis of seroprevalence	Number of estimated deaths using a 0.5% probability of death	Estimated COVID-19 mortality per million inhabitants	Number of observed deaths (as of June 2)	Ratio of estimated to observed deaths	COVID-19 mortality per million inhabitants
Ile-de-France	12,278,210	10	1,227,821	6,139	500	7,273	0.84	592
Grand-Est	5,511,747	9	496,057	2,480	450	3,565	0.70	647
New-Aquitaine	5,999,982	3.1	185,999	930	155	420	2.21	70
Bouches-du-Rhône	2,034,469	7.96	161,944	810	398	535	1.51	263

255 Focus on two French cities: Paris and Marseille

256 Significant differences, particularly in screening and treatment strategies, were observed 257 between Paris, where outpatients were not tested, and Marseille, where outpatients and asymptomatic people were tested. The cumulative incidence rate of hospitalization was 4,159 258 259 patients per million inhabitants in Paris, which was significantly higher than the rate of 1,196 patients per million inhabitants in Marseille (p-value <0.001) (Figure 4A), suggesting a 260 261 preventive effect associated with broader testing. The number of individuals admitted to the 262 ICU in Paris (959 per million inhabitants) was also significantly higher than that in Marseille (71 per million inhabitants) (p-value <0.001) (Figure 4B); moreover, 798 and 149 COVID-19 263 264 deaths per million inhabitants were observed in Paris and Marseille, respectively (Figure 4C). 265 Four patients (3.1%) (one woman and three men) living in Marseille died under the age of 60, including one patient aged 56 years, 2 patients aged 58 years and one patient aged 59 years. 266 267 These patients had comorbidities: bronchopulmonary large cell lung cancer metastasizing to 268 the brain, diabetes, hypertension, early Alzheimer's disease, or a history of stroke or severe 269 ischaemic heart disease. A large number of missing data on the age of deceased patients in 270 Paris were observed, making analysis of the latter impossible. Paris had an excess mortality of 271 approximately 2,000 patients between 2020 and 2018/2019 (+21.2% vs 2018 and +21.9% vs 272 2019), whereas 384 (+7.7%) additional patients died compared to 2018 and 371 (+7.4%) 273 compared to 2019 in Marseille (Table 3). Moreover, there was a drop between -23.8% and 274 1.7% in mortality in hospice or residential facilities for dependent elderly people in Marseille, 275 which was not the case in Paris (+70.8% vs 2018 and +61.6% vs 2019).



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Figure 4 – A. Weekly cumulative incidence of hospitalization of COVID-19 patients per million inhabitants
in Paris (blue) and Marseille (red). B. Weekly cumulative incidence of intensive care unit (ICU) admission
of COVID-19 patients per million inhabitants in Paris (blue) and Marseille (red). C. Weekly cumulative
COVID-19-associated mortality per million inhabitants in Paris (blue) and Marseille (red).

Table 3 – Excess mortality in 2020 compared to 2018/2019 from January to August in Marseille and Paris. The data were collected from the INSEE

286 database.

	2020 vs 2018					2020 vs 2019				
		Paris	Ma	rseille		Paris	Ma	rseille		
	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)	Ν	Number of excess deaths (% excess)		
Deaths from all causes	9,243	1,961 (21.2%)	5,015	384 (7.7%)	9,192	2 012 (21.9%)	5,028	371 (7.4%)		
Deaths from all causes in public or private hospitals	5,960	806 (13.5%)	2,852	-164 (- 5.8%)	5,830	936 (16.1%)	2,761	-73 (-2.6%)		
Deaths from all causes in hospice or among dependent elderly residents in retirement homes	565	400 (70.8%)	248	59 (23.8%)	597	368 (61.6%)	302	5 (1.7%)		
Deaths from all causes at home	2,319	737 (31.8)	1,732	70 (4.0%)	2,426	630 (26.0%)	1,812	-10 (0.6%)		

288 Discussion

289 Mortality from an epidemic disease depends on several factors, the first being the size of the 290 epidemic, which can be assessed retrospectively by seroprevalence studies. Three countries, 291 namely, Spain, Italy and France, have conducted seroprevalence surveys and showed that 292 locked-down people tended to have more antibodies against SARS-CoV-2 than others, suggesting that they were more prone to be exposed to the virus [18,25,26]. In a second step, 293 294 mortality by age group can be examined in comparable situations. In Figure 1, the natural 295 mortality, observable from three ships with outbreaks of CoV-2-SARS on board, was 296 extremely low, suggesting that in other contexts, mortality should be extremely low in healthy 297 people under 50 years of age [10-12]. Focusing only on mortality in the under-60 age group, 298 we observed that mortality was lower in Spain and Germany than in France. It was extremely 299 low in patients seen at Marseille IHU and significantly lower still in those who received 300 hydroxychloroquine and azithromycin treatment in all age groups [27]. This also translates 301 into a decrease in all-cause mortality in the Southern region of France compared to France 302 overall. Particularly, in the Ile-de-France region, the mortality rate among people under 60 years of age was twice that in the Southern region. Finally, if we project the estimated number 303 304 of deaths obtained by multiplying lethality by seroprevalence, the model very clearly shows 305 excess mortality in the Ile-de-France and Grand Est regions compared to the Bouches-du-306 Rhône department [28,29]. Overall, it is difficult to dispute that despite similar epidemic 307 levels, there were more hospitalized patients, more transfers to intensive care units and more 308 deaths in Paris than in Marseille, and the correlation of all these parameters suggests that this is not due to chance. 309

Countries in Europe and the Americas unquestionably need to reflect on the management of their COVID-19 epidemics. It appears that the richest countries with the highest level of care have had significantly higher mortality rates than the poorest countries 313 [30,31]. Among the reasons for this difference are the inability to rapidly develop diagnostic 314 tests in our country during the first months of the epidemic; the lack of immediate medical 315 care for patients, which was the consequence of the inability to meet the needs in terms of 316 testing; and the inadequacy of influenza-based recommendations when the disease is very 317 different from influenza (e.g., hypercoagulation problems and happy hypoxia), which led to 318 delays in the care and medicalization of these patients [3,7,9,32,33].

319 Furthermore, we believe that in developed countries, which are less familiar with 320 infectious diseases [31], strategies tending to privilege therapeutic trials over routine care 321 have led to delayed management and less efficient quality of care than in countries where the 322 immediate health of patients was prioritized over therapeutic trials. For example, in China, the 323 idea of not giving specific care was considered unethical, and doctors prescribed antivirals, but no more than three [34]. The strategy in France, by contrast, was to give no treatment until 324 325 its effectiveness had been proven by randomized trials. This difference in strategies between the rich Western world and the rest of the world is probably relevant to the very high 326 327 mortality rate observed in France.

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