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## Temporal and age distributions of SARS-CoV-2 and other coronaviruses, southeastern France

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1 **Temporal and age distributions of SARS-CoV-2 and other coronaviruses, Southeastern**  
2 **France**

3

4 **Short title (for the running head): Temporal and age distribution of coronaviruses**

5

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18

## ABSTRACT

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**Objectives.** The SARS-CoV-2 epidemic presents a poorly understood epidemiological cycle. We aimed to compare the age and weekly distribution of the five human coronaviruses, including SARS-CoV-2 that circulated in southeastern France.

**Methods.** We analyzed all available diagnoses of respiratory viruses including SARS-CoV-2 performed between 09/2013 and 05/2020 at University Hospital Institute Méditerranée Infection in Marseille, Southeastern France.

**Results.** For SARS-CoV-2, positive children <15 years of age represented 3.4% (228/6,735) of all positive cases, which is significantly less than for endemic coronaviruses (46.1%; 533/1,156;  $p < 0.001$ ). Among 10,026 patients tested for SARS-CoV-2 and endemic coronaviruses in 2020, children <15 years represented a significantly lower proportion of all positive cases for SARS-CoV-2 than for endemic coronaviruses [2.2% (24/1,067) vs 33.5% (149/445), respectively;  $p < 0.001$ ]. Epidemic curves for endemic coronaviruses and SARS-CoV-2 in 91,722 patients showed comparable bell-shaped distributions with a slight time lag. In contrast, age distribution of endemic coronaviruses and 14 other respiratory viruses differed very significantly compared to that of SARS-CoV2, which was the only virus to spare children.

**Conclusions.** Thus, we observed for SARS-CoV-2 a temporal distribution resembling that of endemic coronaviruses and an age distribution that spares the youngest subjects who are those the most exposed to endemic coronaviruses.

**Key words:** SARS-CoV-2; endemic coronavirus; age; children; cross-immunity; Southeastern France

44 **INTRODUCTION**

45 The SARS-CoV-2 epidemic, which apparently started in December in China (Wu and  
46 McGoogan, 2020), currently presents a poorly understood epidemiological cycle. It seems to  
47 have had in China, Korea and now in Europe a bell-shaped distribution  
48 (<https://coronavirus.jhu.edu/data/new-cases>; <https://www.mediterranee-infection.com/covid-19/>) as is common for viral respiratory infections. Furthermore, we and others have shown  
49 that detection of SARS-CoV-2 in children is rare, as are clinical cases (Colson et al., 2020;  
50 Gudbjartsson et al., 2020; Jones et al., 2020; Li et al., 2020; Wu and McGoogan, 2020). Thus,  
51 in three large studies, children under 10 years of age accounted for <1%, 0% and 1.3% of  
52 SARS-CoV-2 cases in China (Wu and McGoogan, 2020), Iceland (Gudbjartsson et al., 2020)  
53 and Germany (Jones et al., 2020), respectively. The fate of this epidemic remains unknown,  
54 but we found it interesting to compare the age and weekly distribution of the five human  
55 coronaviruses, including SARS-CoV-2 that circulated in south-eastern France in order to  
56 compare the temporal and age distribution of these different viruses.  
57

58

59 **METHODS**

60 We analyzed all available diagnoses of respiratory viruses including SARS-CoV-2 performed  
61 between September 2013 and May 2020 at the clinical microbiology and virology laboratory  
62 of University Hospital Institute Méditerranée Infection ([https://www.mediterranee-](https://www.mediterranee-infection.com/)  
63 [infection.com/](https://www.mediterranee-infection.com/)) and University hospitals of Marseille, the second largest French city,  
64 Southeastern France. Testing of respiratory samples were performed using the FTD  
65 Respiratory pathogens 21 (Fast Track Diagnosis, Luxembourg), the Biofire FilmArray  
66 Respiratory panel 2 plus (Biomérieux, Marcy-l'Etoile, France), the Respiratory Multi Well  
67 System r-gene (Argene, BioMérieux), or the GeneXpert Xpert Flu/RSV (Cepheid, Sunnyvale,  
68 CA) assays, or by one-step simplex real-time quantitative RT-PCR amplifications as

69 previously reported (Hoang et al., 2019). Diagnosis by reverse transcription-PCR of SARS-  
70 CoV-2 infection was performed as previously described (Amrane et al., 2020). This study  
71 retrospectively analyzed patients' data issued from the hospital information system  
72 (RGPD/APHM 2019-73). Statistics were performed using OpenEpi version 3.01 software  
73 ([https://www.openepi.com/Menu/OE\\_Menu.htm](https://www.openepi.com/Menu/OE_Menu.htm)); a p-value < 0.05 was considered significant.  
74 Moreover, epidemic curves were analyzed by Markov Chain Monte Carlo fitting of five  
75 commonly used distributions with different skewnesses (Normal, Log-normal, Gamma,  
76 Weibull, Gompertz) using R-4.0.1 (<https://www.r-project.org/>). Distributions with the best  
77 goodness-of-fit criteria [Akaike's Information Criterion, (AIC)] were chosen and their  
78 parameters bootstrapped.

79

## 80 **RESULTS**

81 First we analyzed all available diagnoses of SARS-CoV-2 or other respiratory viruses for  
82 141,227 patients. Between January and May 2020, we tested respiratory samples from 80,024  
83 patients for SARS-CoV-2 and found 6,735 (8.4%) positive (Figure 1). In addition, between  
84 September 2013 and May 2020 we tested respiratory samples from 69,752 patients for  
85 respiratory viruses. Of them, 17,673 were tested for endemic coronaviruses (HCoV-229E,  
86 HCoV-NL63, HCoV-OC43, HCoV-HKU1) and 1,156 (6.5%) were positive. For SARS-CoV-  
87 2, positive children under 15 years represented 3.4% (228/6,735) of all positive patients. This  
88 proportion was significantly lower than for endemic coronaviruses (46.1%; 533/1,156; p <  
89 0.001, Chi-square test). In fact, positive patients in each group 0-1 year, 1-5 years, 5-10 years  
90 and 10-15 years represented significantly lower proportions of all positive patients when  
91 considering SARS-CoV-2 than endemic coronavirus infections (Table 1). Compared to  
92 SARS-CoV-2-positive patients, those infected with endemic coronaviruses or other  
93 respiratory viruses were significantly more likely to be <10 years of age (Figure 1). Therefore,

94 this age group accounted for 1.8% of SARS-CoV-2 cases compared to 25.0% (for HCoV-  
95 229E) and 87.0% (for bocavirus) of infections with other respiratory viruses ( $p < 0.05$  for all  
96 comparisons).

97         Second, we analyzed 10,026 patients tested for both SARS-CoV-2 and endemic  
98 coronaviruses between January 1<sup>st</sup> and May 25<sup>th</sup>, 2020. A total of 1,067 patients (10.6%) were  
99 SARS-CoV-2- positive and 445 (4.4%) were diagnosed with endemic coronaviruses. Children  
100 under 15 years of age accounted for a significantly lower proportion of all positive cases for  
101 SARS-CoV-2 than for endemic coronaviruses [2.2% (24/1,067) vs 33.5% (149/445),  
102 respectively;  $p < 0.001$ ] as was the case in each age group: 0-1 year, 1-5 years, 5-10 years and  
103 10-15 years (Figure 2A, Table 2). Only 11 (0.11%) patients were infected with SARS-CoV-2  
104 and an endemic coronavirus. They represented a significantly lower proportion than the  
105 proportion of SARS-CoV-2-positive patients among those negative for endemic coronaviruses  
106 [11/445 (2.5%) vs 1,056/9,581 (11.0%);  $p < 0.001$ ]. None of these 11 patients was under 18  
107 years of age.

108         Moreover, over a one-year period (from June 2019 to May 2020), we observed that  
109 epidemic curves were comparable for the four endemic coronaviruses and SARS-CoV-2  
110 (Figure 2B). Cases of endemic coronavirus increased in December 2019, peaked in mid-  
111 March 2020 and ended in early April, while cases of SARS-CoV-2 increased in early March,  
112 peaked in late March and nearly ended in mid-May. The fitted distributions reflected three  
113 kinds of epidemic curves (Supplementary Figure 1). SARS-CoV-2 fitted with a left-skewed  
114 Gamma distribution (AIC=26345.6). HCoV-OC43 fitted with a quasi-symmetric curve and  
115 Normal distribution (AIC=971.4). Epidemic curves of HCoV-229E, HCoV-NL63 and HCoV-  
116 HKU1 were right skewed and fitted with a Gompertz distribution (AIC= 394.5, 1191.2, and  
117 1861.2, respectively).

118

## 119 **DISCUSSION**

120 In this large study, two elements are particularly noteworthy. First, the temporal distributions  
121 in our geographical area of infections by all coronaviruses are comparable. Thus, all five  
122 viruses have a bell-shaped incidence curve and their circulation stopped in the spring,  
123 suggesting that this is the natural SARS-CoV-2 epidemic pattern. Hence, we can speculate for  
124 temperate countries including Europe that SARS-CoV-2 could reappear seasonally during  
125 winter and circulate epidemically until spring. Alternatively, SARS-CoV-2 might disappear in  
126 the absence of asymptomatic human chronic carriage, like SARS-CoV-1 (Raoult et al., 2020).  
127 Second, the age distribution of SARS-CoV-2 cases spares children considerably, which is  
128 radically different from other coronavirus and respiratory virus infections. Thus, SARS-CoV-  
129 2 is the only one we analyzed that does not significantly affect children. Therefore, its  
130 epidemiology could not be predicted based on previous knowledge of viral respiratory  
131 diseases. The simplest explanation for this difference is that a substantial proportion of  
132 children, and particularly those under 5 years of age, may have acquired immunity to endemic  
133 coronaviruses that infect young children with high frequencies (Raoult et al., 2020; Zhou et  
134 al., 2013). Indeed, there is evidence that part of the population exhibited immune responses  
135 against SARS-CoV-2 before the epidemic, supporting the hypothesis of cross-immunity  
136 between endemic coronaviruses and the new coronavirus. Thus, in the US, circulating SARS-  
137 CoV-2-specific CD4+ and CD8+ T cells were detected in  $\approx 20-60\%$  of unexposed individuals  
138 sampled in 2015-2018 (Grifoni et al., 2020). In the UK, IgG to SARS-CoV-2 were detected in  
139 15% of SARS-CoV-2-uninfected patients with recent HCoV infection and in 10% of SARS-  
140 CoV-2-uninfected pregnant women (Ng et al., 2020). In addition, we detected IgM to SARS-  
141 CoV-2 at titers  $\geq 1:100$  in 9/50 patients with endemic coronaviruses (Edouard et al., 2020). It  
142 is also worth noting that the coinfection rate observed here with SARS-CoV-2 and another  
143 coronavirus was very low (0.1%) and that SARS-CoV-2-positivity was significantly lower

144 among patients positive than negative for an endemic coronavirus, which supports the  
145 hypothesis of a protective cross-immunity.

146 Overall, we believe that this work contributes to the understanding of the  
147 epidemiology of SARS-CoV-2, which has a temporal distribution resembling that of endemic  
148 coronaviruses and an age distribution that spares the youngest subjects who are precisely  
149 those the most frequently exposed to endemic coronaviruses and may have consequently  
150 acquired protective immunity. Susceptibility to SARS-CoV-2 in elderly perhaps reflects the  
151 loss of immunity acquired during childhood, or changes in social organization that occurred  
152 during recent decades. Indeed, a small proportion of people over the age of 50 lived in  
153 communities with very young children, whereas women’s work development has led to a  
154 much earlier socialization of children. Finally, the fact that age distributions for infections by  
155 SARS-CoV-2 and other respiratory viruses differ underscores that real data collection and  
156 real-time analysis are critical in the event of an outbreak to decipher the epidemiology of  
157 emerging pathogens.

158

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166

167 **Ethics.** All data have been generated as part of the routine work at Assistance Publique-  
168 Hôpitaux de Marseille (Marseille university hospitals), and this study results from routine

169 standard clinical management. Access to the patients' biological and registry data issued from  
170 the hospital information system was approved by the data protection committee of Assistance  
171 Publique-Hôpitaux de Marseille (APHM) and was recorded in the European General Data  
172 Protection Regulation registry under number RGPD/APHM 2019-73. This study has been  
173 approved by our institution's ethics committee (N°: 2020-029). The authors have no conflicts  
174 of interest to declare. Funding sources had no role in the design and conduct of the study;  
175 collection, management, analysis and interpretation of the data; and preparation, review, or  
176 approval of the manuscript.

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218

## FIGURE LEGENDS

219

220 **Figure 1. Age distribution of the proportions of patients diagnosed with coronaviruses**

221 **and other respiratory viruses compared to the total population tested**

222 (i) SARS-CoV-2; (ii) Coronavirus-229E; (iii) Coronavirus-NL63; (iv) Coronavirus-OC43; (v)

223 Coronavirus-HKU1; (vi) Human parainfluenzavirus 1; (vii) Human parainfluenzavirus 2;

224 (viii) Human parainfluenzavirus 3; (ix) Human parainfluenzavirus 4; (x) Metapneumovirus;

225 (xi) Rhinovirus; (xii) Enterovirus; (xiii) Paraechovirus; (xiv) Adenovirus; (xv) Influenza A

226 H3N2 virus; (xvi) Influenza A H1N1 virus; (xvii) Influenza B virus; (xviii) Respiratory

227 syncytial virus; (xix) Bocavirus.

228

229 **Figure 2. Number of patients positive for coronaviruses over one year from June 2019**

230 **through May 2020**

231 (i) SARS-CoV-2; (ii) HCoV-229E; (iii) HCoV-NL63; (iv) HCoV-OC43; (v) HCoV-HKU1.

232 X-axis corresponds to weeks and years (week-year).

233

234

235

## TABLES

236

237 **Table 1. Number of cases per age group for all patients tested for SARS-CoV-2 or for**238 **endemic coronaviruses, and proportion of all tested patients per age group**

Age group (years)	SARS-CoV-2				Endemic CoV				P *
	Tested		Positive		Tested		Positive		
	N	% **	N	% **	N	% **	N	% **	
0-1	796	1.0	32	0.5	2 412	14.6	207	17.9	<0.001
1-5	1 453	1.8	40	0.6	1 661	11.3	217	18.8	<0.001
5-10	1 231	1.5	50	0.7	628	4.9	65	5.6	<0.001
10-15	1 197	1.5	106	1.6	366	3.0	44	3.8	<0.001
15-18	1 090	1.4	118	1.8	202	1.6	12	1	0.051
18-25	6 680	8.3	594	8.8	409	3.9	43	3.7	<0.001
25-45	27 059	33.6	2 184	32.4	1 502	14.9	165	14.3	<0.001
45-65	24 487	30.4	2 257	33.5	2 250	18.3	176	15.2	<0.001
65-75	6 545	8.1	560	8.3	1 419	10.3	79	6.8	0.050
>75	9 986	12.4	794	11.8	2 528	17.2	148	12.8	0.175
Total	80 524	100.0	6 735	100.0	17 673	100.0	1 156	100.0	-

239 \* Yates-corrected Chi-square test; \*\* Proportion of cases in the age group compared to the total number of cases

240

241 **Table 2. Number of cases per age group for SARS-CoV-2 or endemic coronaviruses for**242 **patients tested for all five coronaviruses, and proportion of all tested patients per age**243 **group**

Age group (years)	Tested		SARS-CoV-2-positive		Endemic CoV-positive		P *
	N	% ***	N	% ***	N	% ***	
0-1	477	4,8	11	1.0	41	9.2	<0.001
1-5	715	7,1	5	0.5	68	15.3	<0.001
5-10	402	4,0	4	0.4	18	4.0	<0.001**
10-15	270	2,7	4	0.4	22	4.9	<0.001**
15-18	160	1,6	11	1.0	5	1.1	0.454
18-25	590	5,9	75	7.0	25	5.6	0.186
25-45	2 321	23,1	245	23.0	109	24.5	0.283
45-65	2 491	24,8	385	36.1	83	18.7	<0.001
65-75	1 002	10,0	128	12.0	26	5.8	<0.001
>75	1 598	15,9	199	18.7	48	10.8	<0.001
Total	10 026	100,0	1 067	100.0	445	100.0	-

244 \* Yates-corrected Chi-square test; \*\* Fischer exact test; \*\*\* Proportion of cases in the age group compared  
245 to the total number of cases

Fig 1.

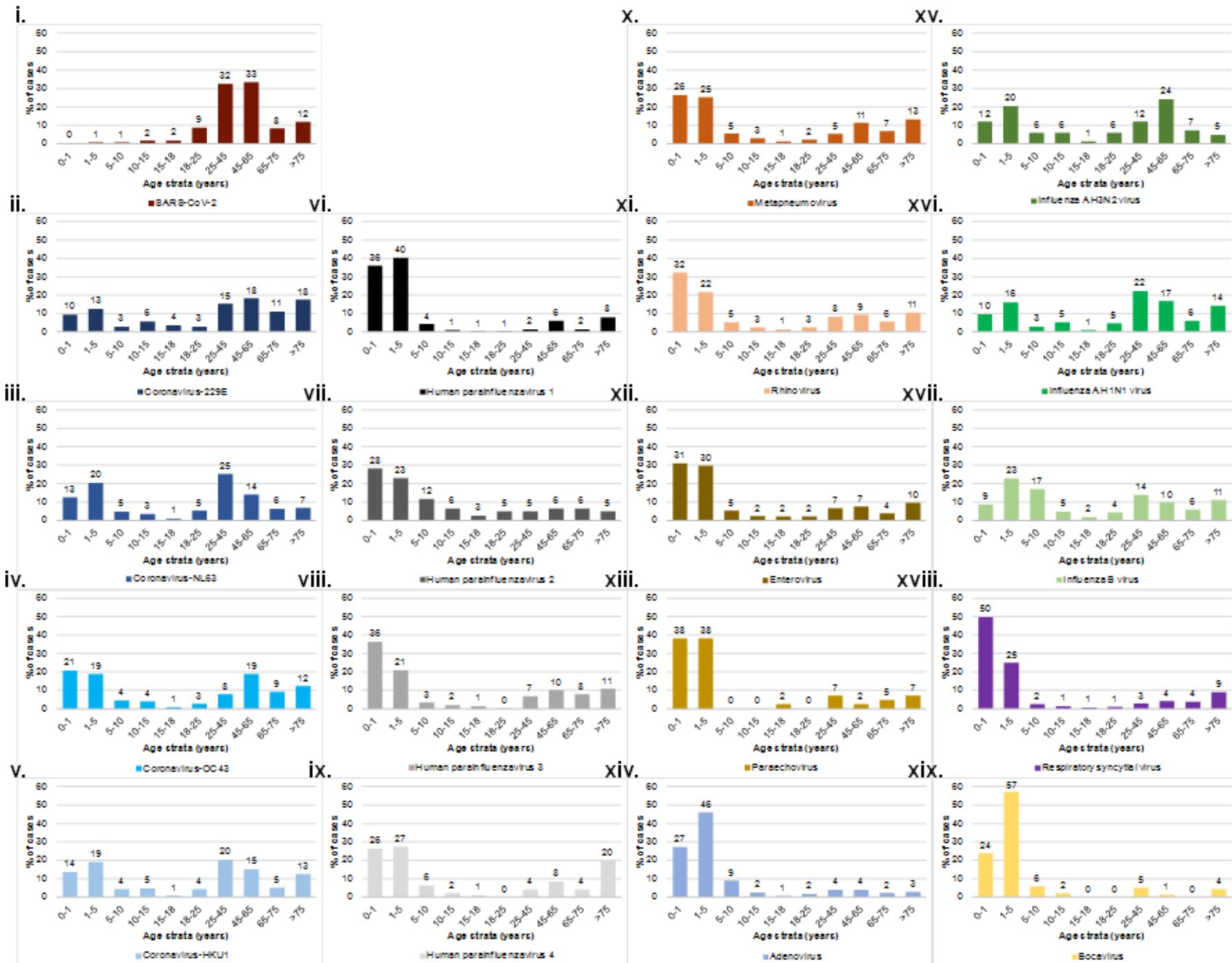


Fig 2.

