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Evolution of SARS-CoV-2: Review of Mutations, Role of the Host Immune System

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1 Evolution of SARS-CoV-2: review of mutations, role of the host immune system

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51 ABSTRACT

52 Since the reporting of the first cases of Covid in China and the publication of the first
53 sequence of SARS-CoV-2 in December 2019, the virus has undergone numerous mutations.
54 In Europe, the spring outbreak (March-April) was followed by a drop in the number of cases
55 and deaths. The disease may have evolved into a milder form. The increase in PCR-positive
56 cases in late summer 2020 did not lead to the expected increase in hospitalizations, ICU
57 admissions and deaths, based on the severity of the disease in the spring. This difference in
58 disease severity could be due to factors independent of the virus or to the evolution of the
59 virus.

60 This review attempts to identify the mutations that have appeared since the beginning
61 of the pandemic and their role in the temporal evolution of the pandemic.

62 There is a cell and humoral type cross-reactivity in a large part of the population to
63 common cold coronaviruses (HCoV)s and SARS-CoV-2.

64 Evolutionarily important mutations and deletions have emerged in the SARS-CoV-2
65 genes encoding proteins that interact with the host immune system. In addition, one of the
66 major mutations (in viral polymerase) is logically associated with a higher frequency of
67 mutations throughout the genome. This frequency fluctuates over time and shows a peak at
68 the time when the epidemic was most active. The rate of mutations in proteins involved in the
69 relationship to the immune system continues to increase after the first outbreak.

70 The cross-reactivity on the one hand and the viral mutations observed on the other
71 hand could explain the evolution of the pandemic until the summer of 2020, partly due to the
72 evolution of the virus in relation to the host immune system.

73 The immunization campaign began in December 2020: concerns are emerging about a
74 possible escape of the circulating variants vaccines in early 2021. These variants could also
75 escape immunity acquired through infection with the 2020 strains.

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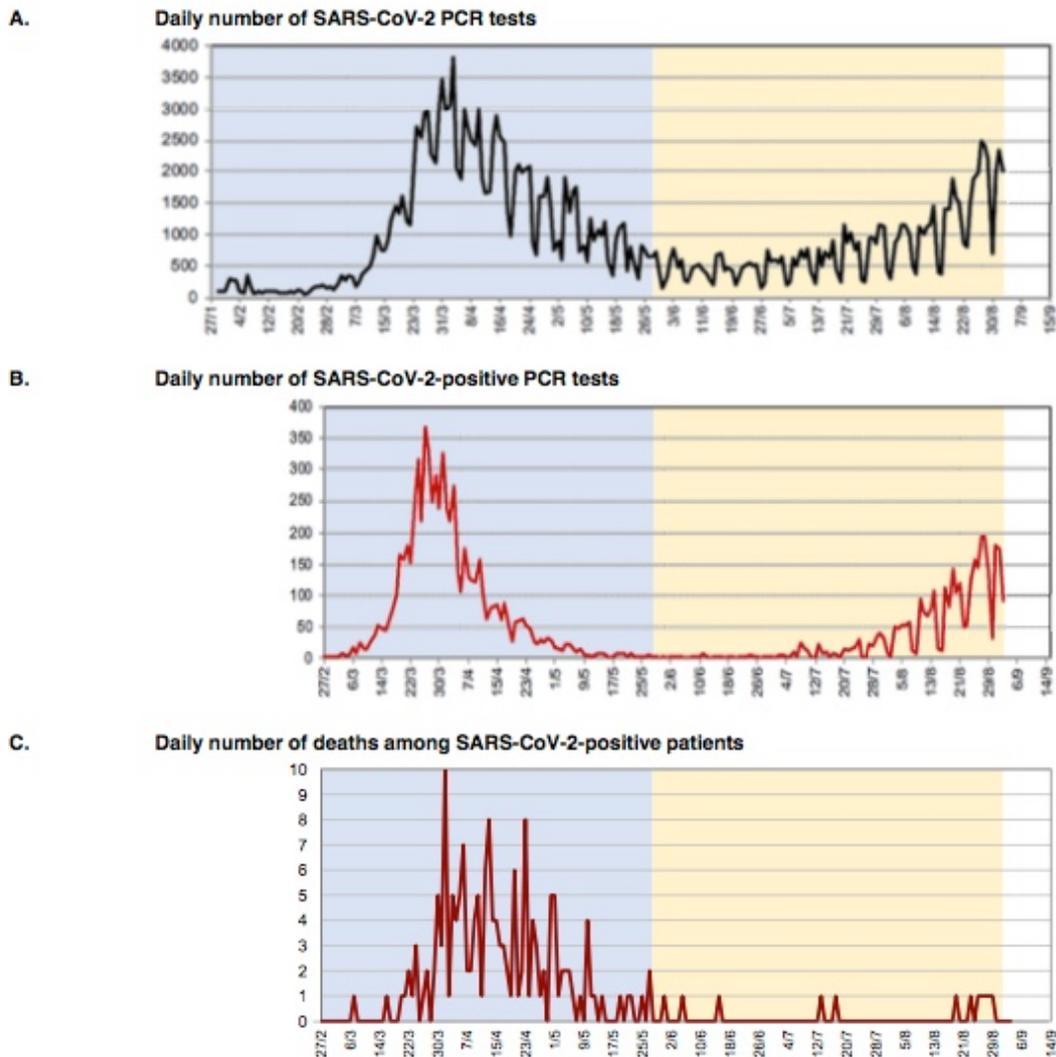
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104 EVOLUTION OF THE EPIDEMIC

105 The SARS-Cov-2 pandemic has been occurring in several phases since the emergence
106 of the virus in China at the end of 2019. In Europe, the spring outbreak (March-April) was
107 followed by a decrease in the number of cases and deaths. According to some physicians who
108 treated Covid-19 patients during the consecutive phases of the outbreak, the virus is believed
109 to have evolved into a milder phenotype from the end of May 2020. But several factors
110 independent of the virus could have impacted the case-fatality rate (number of deaths/case
111 numbers). At the beginning of 2020, testing capabilities were poorly developed. Mask use
112 was not widespread and its use became widespread late, which may have reduced the
113 inoculum of infected persons and the severity of cases, and the clinical management of
114 COVID-19 had to improve over time.

115 However, this is not the case everywhere: according to the IHU Marseille (France) [1], the
116 mortality of patients hospitalized since mid-June is lower than that of the March-April phase.

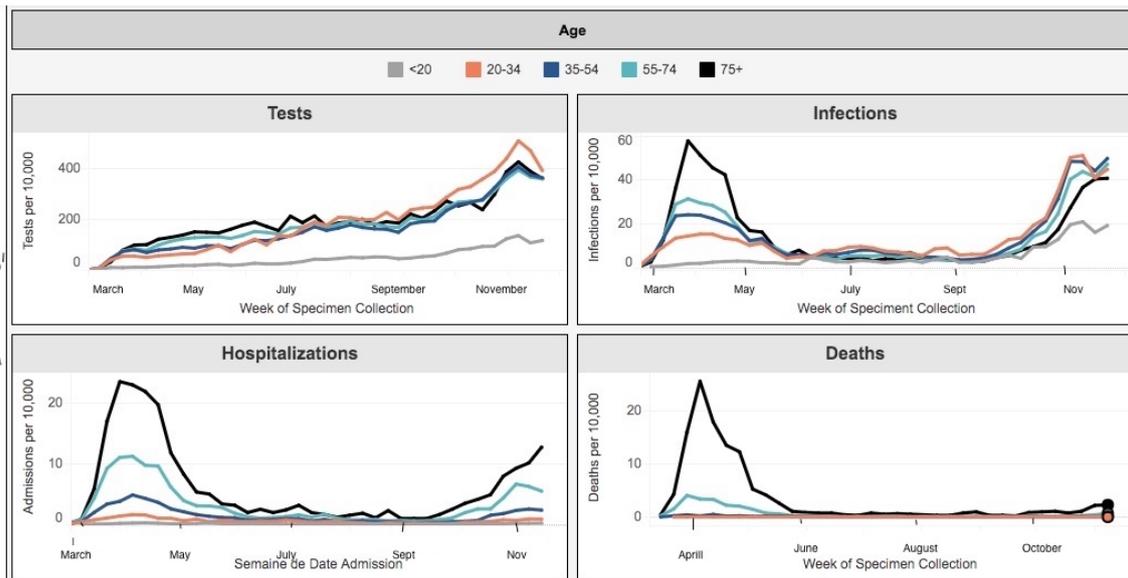
117 This cannot be due to a bias in the comparison of the mortality rate between these two periods
118 because the strategy of testing and clinical and therapeutic management has remained the
119 same Figure1.



120
 121 Figure 1 (from Colson et al. [1] : Number of PCR tests, positive diagnoses, and deaths from
 122 February to September.

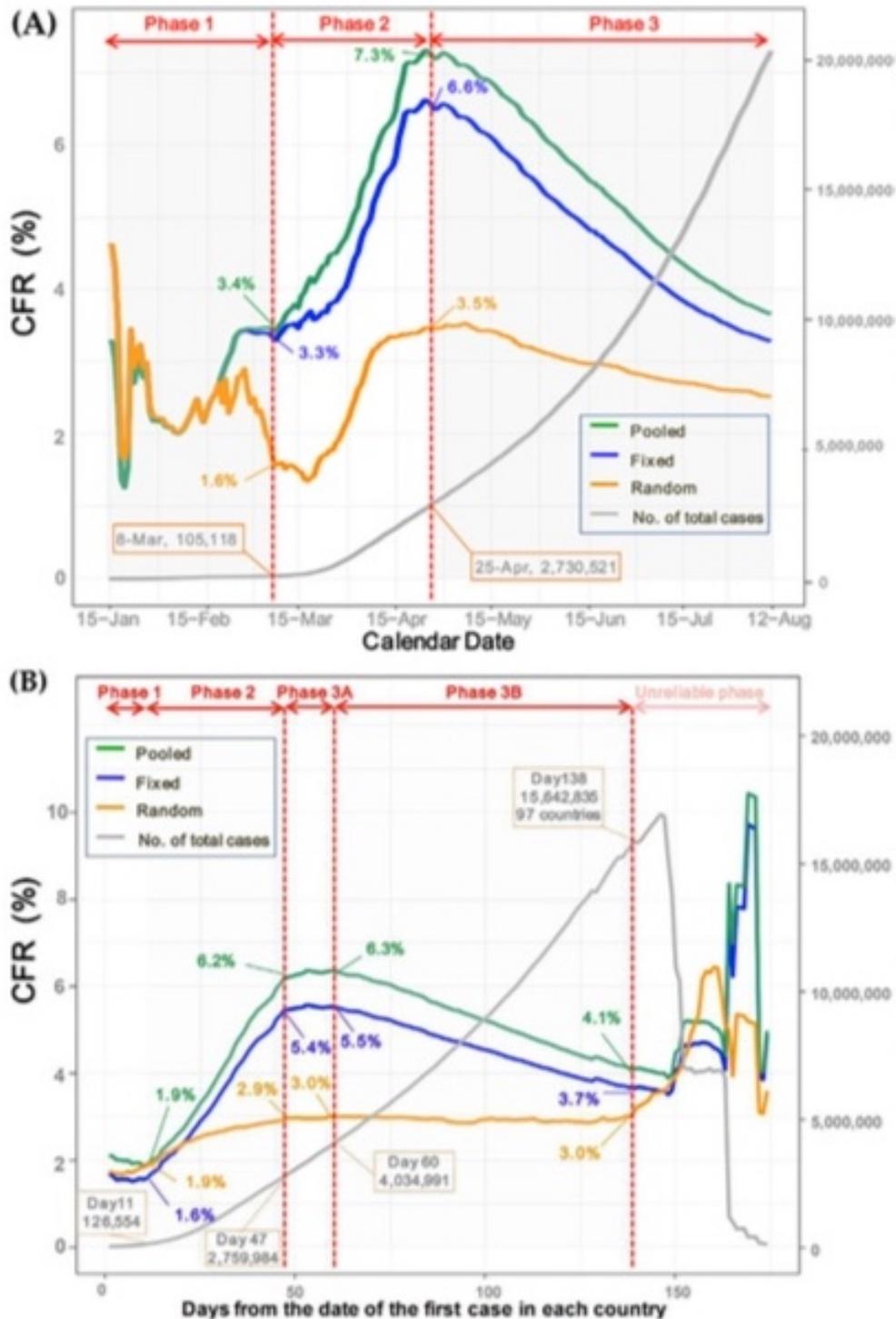
- 123 A. Number of PCR tests performed at IHU Méditerranée Infection;
 124 B. Number of PCR- positive patients performed at IHU Méditerranée Infection;
 125 C. Number of deaths among SARS-CoV-2-positive patients in Marseille public hospitals
 126 (Assistance Publique-Hôpitaux de Marseille).

127
 128 In Philadelphia (Pennsylvania), where the massive testing campaign started late, in contrast to
 129 Marseille (France), the curves of positive cases, hospitalizations and deaths also show this
 130 epidemic peak in March-April followed by a very clear decline. The increase in
 131 hospitalizations and deaths at the end of the summer is also not proportional to the number of
 132 infections, fig2.



133
 134 Figure 2: ([https://www.phila.gov/programs/coronavirus-disease-2019-covid-19/testing-and-](https://www.phila.gov/programs/coronavirus-disease-2019-covid-19/testing-and-data/#/)
 135 [data/#/](https://www.phila.gov/programs/coronavirus-disease-2019-covid-19/testing-and-data/#/)) Number of tests performed, infections, hospitalizations and deaths between March
 136 and November 2020, Philadelphia, Pennsylvania.

137
 138 According to Ghayda *et al.* [2], who evaluate the best way to estimate the case-fatality rate
 139 dynamically as the epidemic evolves, the case-fatality rate would appear to decrease
 140 regardless of the evaluation method. Fig.3.



141
 142 Figure 3 : Timeline of CFR worldwide among countries with COVID-19 reports until August
 143 12, 2020: (A) According to date and (B) According to days since the first confirmed case.
 144 COVID-19: Coronavirus 2019, CFR: case fatality rate, Fixed: fixed-effect model, Random:
 145 random-effect model, Pooled: calculated CFR based on incidence and mortality data, N:
 146 number. Gayda *et al.* [2]
 147 Wesley *et al* [3] have proposed that RNA viruses undergo natural genetic attenuation that
 148 contributes to the transient nature of pandemics caused by these viruses. Hygiene measures

149 (such as the physical distancing provided by wearing masks) and host immune defences
150 (partial immunity that may result in the case of Covid-19 from cross-reactivity with HCoV-229E)
151 would reduce inoculum levels and accelerate the mutation rate, which should result in greater
152 bottlenecks and accelerated decline.

153 The emergence of another human coronavirus, HCoV-OC43 has been proposed to be linked
154 to a host change around 1890, a time that coincides with a pandemic of respiratory disease in
155 humans (4).

156 Could SARS-CoV-2, responsible for Covid-19, follow this evolutionary path as suggested by
157 Benedetti *et al.*[5] ?

158

159 CROSS REACTIVITY BETWEEN SARS-CoV-2 AND HCOVs

160

161 Cross-reactivity to common cold viruses and SARS-CoV-2 is now established [6].
162 This reactivity is logically directed against antigens common to all coronaviruses and not
163 against SARS-CoV-2 specific antigens. These common antigens are found on the structural
164 proteins N, M and Spike and also on non-structural proteins (NSPs, including viral RNA
165 replication enzymes). Important differences in cellular reactivity to coronavirus epitopes are
166 found between exposed and unexposed individuals and between severely affected and
167 asymptomatic or poorly affected individuals. According to Grifoni *et al.* [7], the unexposed
168 preferentially (compared to the exposed) reacts to ORF1 proteins (open reading frame = area
169 of the genome that codes for many overlapping proteins) whereas the exposed recognize
170 structural proteins ; according to Mateus *et al.* [8], epitopes of M (the membrane protein) are
171 not recognized by the unexposed, whereas they are recognized in a robust way in Covid
172 (CD4+) cases. Li *et al.* [9], also did not find the same type of cellular response according to
173 the severity of the disease in 2003 SARS-CoV.

174 Non-structural proteins are highly conserved among coronaviruses. According to Le
175 Bert *et al.* [10], exposed but uninfected individuals would develop cellular reactivity towards
176 NSPs involved in viral RNA replication, in particular NSP1 (encoded by the Orf1 region).
177 Indeed this protein is essential for virus replication, and is therefore expressed first.

178 Therefore, ORF1-specific T cells could hypothetically interrupt viral production by lysing
179 SARS-CoV-2 infected cells before the formation of mature virions. NSP1 is involved in
180 escape to the host immune system (it blocks innate immunity and interferon synthesis)[11].

181 While most of the scientific literature assumed pre-existing T cells could be beneficial, there
182 is also the possibility that pre-existing immunity might actually be detrimental (Sette and
183 Crotty [12]. According to Bacher *et al.* [13], cross-reactive T cells have a low avidity,
184 negatively impacting the response quality against neoantigens such as SARS-CoV-2 and
185 inappropriate immune reactions. But these authors suggest that pre-existing memory T cells
186 targeting HCOVs epitopes and having a low cross-reactivity with SARS-CoV-2 epitopes
187 could prevent the activation of naïve T cells and the selection of high affinity clones. This is
188 inconsistent with the documented presence of cross-reactive T cells in all donors exposed or
189 unexposed to Covid-19 and with the fact that the majority of individuals infected with SARS-
190 CoV-2 have a mild or asymptomatic infection. If there is a harmful role for these low affinity
191 memory T cells it appears to correlate with the immunological age of the patient. Moreover,
192 according to Sagar *et al.* [14], a recent HCoV infection would protect against a severe Covid.

193

194 According to Kevin *et al.* [15], antibodies directed against the S2 subunit of the spike protein
195 of SARS-CoV-2 would pre-exist in many uninfected subjects, they would come from
196 previous HCoV infections. In Africa, where Covid has had little effect, Tso *et al.* [16], find a
197 predominance of cross-reactive antibodies directed against the N protein. The prevalence of

198 these antibodies is 6-8 times higher than that found in the USA where the incidence and
199 morbidity of Covid has been higher.

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202

203 EVOLUTION OF THE VIRUS

204

205 It seems that the emergence of the virus dates back to late summer 2019 in China, and that the
206 virus entered the West as early as October 2019 (or earlier?). This is suggested by Li Y. et al.
207 [17] based on mutation analysis. Van Dorp et al. [18] indicate that the disease spread
208 worldwide probably from the beginning of the pandemic. Chaw et al. [19] also believe that
209 SARS- CoV-2 circulated cryptically well before the late 2019 outbreak in China, Gambaro F
210 et al. [20] say the same for France.

211 A hypothesis on the origin of SARS-CoV-2, discussed by Sallard et al. [21], proposes that
212 SARS-CoV-2 is derived from a virus that appeared in a mine in China in 2012, was collected
213 in a laboratory and may have escaped from it during manipulations in 2018 or 2019 . This
214 hypothesis could account for the circulation of the virus before the outbreak, during this early
215 period the virus could have undergone undetected mutations. Thus, there would be a lack of
216 archives from the early period of the pandemic and mutations that occurred during this period
217 would have gone unnoticed. Moreover, only a few tens of thousands of sequences have been
218 analyzed out of the 34 million suspected cases of Covid-19. Of the 295 000 published
219 sequences (Gisaid <https://www.gisaid.org>) a minority were analyzed for their biological and
220 evolutionary significance. It will therefore be necessary to follow in the coming months the
221 publications on late phase isolated sequences.

222 What are the main mutations found on SARS-CoV-2 compared to the first published Chinese
223 sequence dated December 2019? This work will be mainly limited to the first two phases of
224 the pandemic (from December 2019 to summer 2020).

Genome region	Protein	Mutated nucleotide	Remark	Role or assumed role
Leader 5'UTR		C251T	G clade	not transcribed
		Mutated amino-acid		
<i>orf1ab</i>	NSP1		excess of mutations	Immune evasion
	NSP2	T265I		
	NSP3	F106F	G clade silent	inflammasome interaction
	NSP6	L37F	V clade	innate immunity interaction
		L3606F		
	NSP12	P323L	G clade	RNAdependentRNAPolymerase
	NSP13	P504L		Helicase
		Y541C		
	NSP14			Exonuclease proofreading
Spike	S	D614G	not in RBD G clade	increase infectivity increase viral load URT
		N439K	in RBD	increase infectivity
		deletions		
<i>orf3a</i>	viroporin	Q57H	USA	cellular release of virus
		G215V	V clade (China)	replication virulence
<i>orf8</i>	ORF8	L84S	S clade	host immune response
		deletions		immunogenic protein
Nucleocapside	N	R203K	GR clade	increase infectivity
		R202K	these 3 mutations are linked	and replication
		G204R		
<i>orf10</i>		deletions		non coding region not essential

225

226 Table 1: Main mutations and deletions.

227

228 Deletions

229 They are mainly found in regions coding for proteins that interact with the host
230 response and in the spike protein.

231 A hotspot of deletion in the Nsp1 region has been found in several countries,
232 suggesting that it is due to potential convergent evolution. Particularly the Δ 500-532 is
233 correlated with lower viral load, non severe traits and lower serum IFN- β , with possible
234 implications for proper immune response against SARS-CoV-2 infection [22]

235 In April 2020 [23], a deletion is found in the *orf7* region (Orf = open reading frame)
236 from the original sequence. It concerns a region that could be important for the adaptation of
237 the virus to humans (because it is close to the *Orf8* region identified in 2003 for SARS-CoV-1
238 [24].

239 Between January and February 2020, a team from Singapore recovered a deletion of
240 382 nucleotides in the *Orf8* region [25]. The authors suggest that the deletion could lead to an
241 attenuated SARS-CoV-2 phenotype. This mutation then disappeared after March 2020.

242 Hospitalized patients with this mutation had less severe Covid than those without it. The
243 *Orf8* region is believed to be involved in immune evasion.
244 Patients carrying this variant have better T cell responses and higher production of gamma
245 interferon. The proteins produced by *orf8* are highly immunogenic and induce early antibody
246 synthesis during the disease. The absence of these proteins in patients carrying the mutation
247 could explain the lesser inflammatory response.

248 This deletion could have been selected by the pressure of the host immune system:
249 Muth D. *et al.* had already proposed this for a deletion in ORF8 found on a strain of SARS-
250 CoV-1 [24].

251 McCarthy *et al.* highlight [26] the importance of deletions in immune evasion on the
252 evolutionary trajectory of SARS-CoV-2 to an endemic virus. According to Parvez *et al.* [27]
253 and Rahman *et al.* [28], deletions in ORF7, ORF8 and ORF10 found in Bangladesh were
254 associated with reduced virulence. According to Liu *et al.* [29], isolates containing deletions
255 in or near the furin polybasic site of the spike protein have been associated with mild or
256 asymptomatic outcome. Variants with deletions may be under-represented in the databases
257 due to their low frequency and thus their elimination, Nagy *et al.* [30]. Moreover, very few
258 complete sequences have been deposited at GISAID, Wang R *et al.* [31].
259

260 Observed mutations

261 The selected point mutations (SNPs) would be in epistatic interaction: they are the signatures
262 of the observed clades which present distinct spatial and temporal dynamics [32]. According
263 to Rice *et al.* [33], untranscribed regions are subject to selection (*orf10* for example).
264 According to Nagy *et al.* [30], the absence or modification of a NSP and non-transcribed
265 regions can influence the expression of the viral genome and have as much effect on
266 pathogenicity as non-synonymous mutations.

267 Below will be listed possible correlations between point mutations and disease
268 severity and/or infectivity. But it should be kept in mind that SNPs have co-evolved to form
269 the clades that have become dominant and these associations of synonymous and non-
270 synonymous mutations and deletions could strongly influence fitness and virulence.
271

272 Mutations on the Spike protein (D614G and others)

273 The D614G mutation (located outside the RBD-receptor binding domain) resulted in
274 the replacement of an asparagine by a glycine on the C-terminal part of the surface spike
275 protein. This mutation never appears alone but is part of a haplotype of 4 mutations (including
276 those that alter NSP12 (NSP = non-structural protein), 5' TRU, and silently NSP3), which
277 constitute the clade G originating from China and established in Europe [34].

278 It is not certain that this mutation increases infectivity but it is now accepted that it does not
279 increase the severity of the disease [35]. However, in April 2020 (first phase of the pandemic)
280 Becerra-Flores and Cardozo noted a correlation between the frequency of the D614G variant
281 and the case-fatality rate [36], although this kind of analysis can be complicated by different
282 availability of testing and care in different nations [35]. Wesley *et al.* [37] validate previous
283 studies showing that patients infected with variant D614G have higher viral loads in the upper
284 respiratory tract without worsening the disease. Plante *et al.* propose that strains carrying
285 D614G would be less adapted to the lower respiratory tract [38].

286 Other mutations appeared during the summer in the spike protein, in particular N439K in
287 RBD: according to Chen J *et al.* [39], the most frequent mutations in the spike (including
288 D614G, N439K and S477N) increase its transmissibility. A strain with D614G associated
289 with mutations at RBD is more infective and resistant to some neutralizing antibodies with
290 obvious implication for the recovery of COVID-19 patients [40].
291

292 Mutations related to the host immune system

293

294 Wang R *et al.* [41] show by studying C>T mutations in the viral genome that about 65% of
295 these are imposed by the host immune response: the APOBEC system (apolipoprotein B
296 mRNA editing enzyme, catalytic polypeptide-like) edits the viral genes and in return T>C
297 mutations are caused by the virus' protection mechanism, T>C.

298 This C>T ratio increases with age (older people are more affected) and may also explain the
299 differences in the populations' level of infection (Africans and Oceanians are less affected by

300 this mutation and the epidemic in their geographical area has been less severe than
301 elsewhere).

302 According to Rice *et al.* [33], this codon bias could be a route to attenuation of the virus
303 through reduced immunogenicity.

304

305 Jaroszewski *et al.* [42] showed an excess of mutations in proteins Nsp1, Nsp2 and in Orf3a,
306 Orf8b, Orf14 (involved in virus-host interactions) compared to other sites. The spike, the
307 membrane M protein and RdRp (RNA dependent RNA polymerase virale = Nsp12)
308 show a lower rate of false-sense mutations compared to the others: this would be due to the
309 purifying selection effect given the importance of RdRp for the biology of SARS-CoV-2.
310 The Nsp1 protein allows immune evasion of the virus [11] a mutation in this location can
311 make the virus vulnerable to immune clearance. Nsp1 plays a role in inhibiting host RNA
312 expression [43] and in IFN- β response, as seen above [22]. Exposed and unexposed
313 individuals have a different T cell response to the NSP1 protein [10].

314 NSP3 could be involved in the cytokine releasing inflammation observed in severe Covid;
315 this protein would interact with the inflammasome (protein complex involved in inflammation
316 and innate immunity) and in particular through its hypervariable part. The expression of the
317 NSP3 protein in IFN-activated macrophages (IFN : interferon) would indirectly promote
318 prolonged pro-inflammatory expression of IFN-stimulated genes. This would participate in
319 the cytokine storm characteristic of severe cases of COVID-19 [44].

320 The synonymous mutation in NSP3 (F106F) has co-evolved with the other signature
321 mutations of clade G and could, although silent, affect the fitness of the virus [34].

322 According to Wang *et al.* [45], the NSP6 L37F mutation, frequently found at the beginning
323 of the pandemic, mainly in Asia, is associated with a high frequency of asymptomatic cases.
324 However, it disappeared in the later phases of the pandemic and belonged to the GISAID
325 clade V [46]. NSP6 decreases the autophagic capacity of infected cells, which provides an
326 innate defense against viral infections. This capacity also promotes cell death and morbidity.

327 The Q57H mutation is found on the Orf3a region, Wang *et al.* [47].

328 ORF3a proteins are involved in apoptosis and activate the inflammasome. The ORF8 protein
329 is involved in immune system evasion: the temporal evolution of the L84S mutation, which
330 mainly appeared in the USA and is associated with two other helicase mutations (NSP13,
331 P504L, Y541C), follows the evolution of deaths in the first phase of the epidemic (March to
332 June 2020). The Y541C and P504L mutations would prevent the SARS-CoV-2 from
333 interacting effectively with the host interferon signaling molecules and NSP13 from
334 participating effectively in the replication/transcription process.

335 On the contrary, according to Nagy *et al.* [30], mutations associated with a lower result were
336 localized in the surface (S) glycoprotein, in RoRp, in exonuclease 3'-5', in ORF3a, NSP2 and
337 N. Mutations associated with a low result were localized in ORF8, NSP6, ORF3a, NSP4 and
338 in nucleocapsid phosphoprotein N. However, only isolates associated with clinical data were
339 studied (10% of the total published sequences) and the geographical distribution of the
340 sequences obtained is unbalanced (very few come from America and Africa, the majority
341 from Asia). This could bias the results.

342 As Wang *et al.* [45], Banerjee *et al.* [48] and Pachetti *et al.* [49] find spatial-temporal
343 variations as well as Zhao *et al.*[50] for whom the incidence of some of these sites decreased
344 after reaching a (often local) peak. This could indicate a potential signal for positive selection
345 in genes encoding ORF1ab and structural proteins. Mutations in NSP6, NSP13, ORF3a and
346 ORF8 show high-frequency peaks at the beginning of the epidemic and only in some regions,
347 but have subsequently declined sharply and are now low.

348 On the other hand, the frequency of mutations in Nsp2, Nsp12, ORF3a 57, N and S has
349 increased since their introduction into the viral genome. They are present in great abundance
350 in the second half of March, either globally or in certain continents.
351 Eskier *et al.* [51] also study the temporal evolution of the co-mutations of the G and GH
352 clades, unlike Europe, North and South America, where RdRp-P323L became the dominant
353 form with its co-mutations, RdRp323 and its co-mutations remained the minor form in Asia,
354 which may explain the epidemiological differences between these continents.
355 The results suggest that SARS-CoV-2 genomes with the RdRp-323 mutation are 1.5 times
356 more likely to have high mutation rates in other parts of the genome in terms of time and
357 location: a more error-prone mutant RdRp should increase viral genetic diversity and allow
358 the virus to spread under different selective pressures in different populations.
359 Mutations in NSP14, an error-correcting protein exonuclease [41] are most strongly
360 associated with an increased mutation load throughout the genome.
361 Finally, there is a relationship between SARS-CoV-2 mutation densities and the dynamics of
362 viral transmission in human populations, when the number of new daily cases started to reach
363 a plateau. The increase in mutation density ended when the number of new daily cases began
364 to reach a plateau. But synonymous and non-synonymous mutations in the *S* and *orf1a* genes
365 continued to accumulate until the number of cases and deaths declined sharply. According to
366 Alam *et al.* [52], the progression of the pandemic and the number of deaths is correlated over
367 time with the frequency of G clades, and then GH and GR derived from it. The exponential
368 increase in deaths during the first phase of the pandemic is correlated with the frequency of G
369 clade except in the Western Pacific zone. The GR clade is significantly associated with a low
370 death/case ratio. The progression of the disease and the death/case ratio leads to infer an
371 adaptation of the virus (fitness would compromise the virulence of the virus).
372 Tomaszewki *et al.* [34] also studied the rate of mutations in the SARS-CoV-2 genome
373 between January and May 2020. Between January and April, the mutation rate increased and
374 then slowed for Spike and NSP12 and NSP13. Conversely, certain regions of the genome
375 have a mutation rate that continues to increase after April: this concerns the N protein
376 (particularly the R203K and G204R mutations) and viroporin 3a (encoded by *orf3a*, Q57H
377 and G251V mutations). These viral molecules can subvert the immune response, in particular
378 the response to interferon: protein N, protein 3a and NSP6 are antagonists of interferon β
379 which operate in coronavirus diseases.

380

381 EXPLANATORY ASSUMPTIONS

382

383 As demonstrated by Wang *et al.* [41], the majority of SARS-CoV-2 mutations are imposed by
384 the APOBEC antiviral defense system and have *a priori* no adaptive value. The evolution of
385 emerging viruses results from selective pressures (adaptation to the host immune system,
386 increased transmissibility) but most mutations are selectively neutral or slightly deleterious.
387 According to Chen *et al.* [39], mutations on the spike protein all increase transmissibility.
388 As described above, no single SNP studied in isolation is clearly associated with a difference
389 in disease severity. However, deletions on proteins interacting with the immune system could
390 easily go unnoticed (on ORF7 and 8). Clades that have become dominant are characterized by
391 associations of synonymous and non-synonymous mutations (and possibly deletions): positive
392 selection could have selected these associations. For example, the silent mutation (because on
393 an untranscribed region) on the leader 5'UTR (C251T) is part of the signature of the clade G
394 that has rapidly become dominant overall [52].
395 In addition to the pressure on transmissibility, the selective pressure that can act globally on
396 the evolution of the virus is that of innate and pre-existing immunity (perhaps by cross-
397 reaction with other coronaviruses). Indeed adaptive immunity plays a much less important

398 role because it appears later, once the infected person has been able to eventually transmit the
399 virus.
400 Severely ill people fought the virus ineffectively, but those exposed but not ill destroyed most
401 of the infecting virus and were able to select the less virulent (less efficiently replicating)
402 forms not affected by the innate immune system. Indeed, immunopathological phenomena
403 seem to be responsible for the severity of the disease [6]. Virions that stimulate these
404 phenomena less, by interacting less with innate immunity, would be selected and the virus
405 would evolve towards a benign phenotype.
406 Most of the available sequences were isolated from severely ill patients [20].
407 In asymptomatic patients (the majority of infected individuals), few complete sequences are
408 isolated and therefore little is known about the mutations responsible for this attenuation. But
409 we can assume that these "less aggressive" viruses are finally the ones that circulate the most in
410 the general population now, to the point of completely supplanting the "more aggressive"?
411 The work of Eskier *et al.* [51] Wang *et al.* [45] and Tomaszewski *et al.* [34] would tend to
412 show that mutations favoring the virus can also disadvantage it: RdRp makes more errors
413 when it is faster. If these mutations are associated with mutations on the Nsp14 that repairs
414 these errors, mutations in structural proteins may accumulate that could also explain the
415 decline of the epidemic. The variation in the mutation rate of the dominant strains in Europe
416 and the USA is correlated with the temporal evolution of the epidemic : this concerns
417 mutations related to the immune system especially in the declining phase of the epidemic.
418

419 420 CONCLUSION

421
422 It is not impossible that the known common cold coronaviruses, when they jumped from
423 animals to humans (they are all originally responsible for zoonoses), began their evolutionary
424 course with a pandemic like Covid-19. But at the time, the means of investigation in virology
425 and molecular biology did not exist and were not identified.
426 There is a cross-reactivity of cellular and humoral type in a large part of the population to
427 common cold coronaviruses and SARS-CoV-2. Vijgen *et al.* [4] proposed that the common
428 cold coronavirus HCoV-OC43 may have followed the same trajectory as the SARS-CoV-2: a
429 species jump resulting in a pandemic, followed by an evolution to a more benign common
430 cold coronavirus.
431 This evolution seems to be common to emerging viruses (viral attenuation). Evolutionarily
432 important mutations have appeared in the SARS-CoV-2 genes encoding proteins that interact
433 with the host immune system. One of the major mutations (in viral polymerase) is logically
434 associated with a higher frequency of mutations throughout the genome. This frequency
435 fluctuates over time and peaks at the epidemic peak in the spring of 2020.
436 Cross-reactivity on the one hand and the viral mutations observed on the other hand could
437 explain the evolution towards a benign phenotype of SARS-CoV-2, in part by evolution of the
438 virus against the host immune system, at least until the summer of 2020.
439 Sustained attention will need to be paid to mutations that could reduce the efficacy of
440 vaccines (directed against spike protein) [53] and PCRs depending on the probes used [54].
441 In December 2020 a new variant was identified in the UK (VUI 202012/01 or B.1.17),
442 defined by multiple mutations in the spike protein ($\Delta 69-70$, $\Delta 144$, N501Y, A570D, D614G,
443 P681H, T716I, S982A, D1118H). This variant would not be associated with more severe
444 infections, would not preferentially affect an age group compared to previously circulating
445 viruses, but being more contagious it resulted in January 2021 in the highest mortality rate in
446 the UK since the start of the pandemic [55].

447 The B.1.1.7 variant is unlikely to escape recognition by antibodies generated by prior
448 infection or the vaccines [56], although a recent report suggested that the full set of Spike
449 mutations present in the B.1.1.7 variant may reduce the neutralizing activity of the Pfizer
450 vaccine BNT162b2 [57].
451 In December 2020 the variant B.1.351 (501Y.V2) was first isolated in South Africa, it carries
452 8 characteristic mutations in the spike protein [58] and may have increased transmissibility,
453 but no change in disease severity has been shown to date. It has been identified in several
454 European countries [59].
455 Of note, recent statements by Johnson & Johnson [60] and Novavax [61] reported that vaccine
456 efficacy may be reduced against the South Africa variant. Viral neutralisation by sera induced
457 by the ChAdOx1 nCoV-19 coronavirus vaccine against the B.1.351 coronavirus variant were
458 substantially reduced when compared with the original strain of the coronavirus [62].
459 The P.1 variant has so far only been identified in Brazil, and in travelers from Brazil reported
460 in Japan and South Korea. This variant includes 20 unique mutations, some of which could be
461 responsible for an escape of the antibodies [63].
462 Several data are emerging regarding the effect of SARS-CoV-2 mutation on neutralizing
463 antibodies in convalescent patients with possible implication for disease recurrence. Lineage
464 501Y.V2 exhibits complete escape from three classes of therapeutically relevant monoclonal
465 antibodies [64], and serum antibodies [65]. In lineages carrying the E 484 mutation (present
466 in South Africa and Brazil variants), neutralization by some sera is reduced >10 fold [66].

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