Could SARS-CoV-2/COVID-19 simply fade away?

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Since its emergence in Wuhan, China, on November 2019, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been progressively invading every corner of the world. As of today (April 30), it is responsible for more than 3.2 million confirmed cases and more than 220 thousand deaths in 186 countries [1]. SARS-CoV-2 belongs to the enveloped, positive-sense, single-stranded RNA (+ssRNA) *Coronaviridae* family of viruses, which includes at least 49 different species [2]. Coronaviruses are known to infect both birds and mammals, usually producing either respiratory or gastrointestinal diseases [3]. Two previous highly pathogenic outbreaks of coronavirus infections have occurred during the last decades: severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak which started in China in 2003, and Middle East Respiratory Syndrome coronavirus (MERS-CoV), first identified in Saudi Arabia in 2012 [4, 5]. Both of those had a fast expansion and a relatively high case fatality rate (CFR), but after being subject to crucial public health interventions to control their dissemination disappeared rapidly. Before a vaccine could be developed, both diseases tended to fade away.

Like other RNA viruses, coronaviruses have a high mutation rate, around two orders of magnitude higher than DNA viruses [3]. Their genomic mutation rates, estimated by the average number of mutations each offspring will have compared to the parental (or ancestral) genome, are higher. By some estimates, a typical SARS-CoV-2 strain could have around 25 mutations per year, somewhat less than seasonal flu, which has a mutation rate of almost 50 mutations per year [6]. On a per-site level, DNA viruses typically have mutation rates on the order of 10^{-8} to 10^{-6} substitutions per nucleotide site per cell infection; for RNA viruses, however, that range would be between 10^{-6} and 10^{-4} [3]. Some of these mutations would be lethal, and the virus would be unable either to replicate or to infect the host. The possibility of a mutation that would increase the already very high pathogenic capacity of the virus must have happened, perhaps only once, in the evolutionary history of SARS-CoV-2, but would currently be meagre. Many mutations would have little or no effect on the infective capacity of the virus, and would simply explain the genomic variations identified in different strains worldwide [7]. But some of this high mutation rate might be associated with what has been described as mutational degeneration in RNA viruses, which has been studied in SARS since 2002 [8, 9]. Increasing the rate of mutation accumulation ("lethal mutagenesis") could be a pharmacological mechanism to control viral epidemics by accelerating strain extinction [9, 10].

There could be, we speculate, a number of these mutations that could compromise the aggressive behaviour of the virus, leading either to a reduction in the effective reproductive rate (R_t) or in the amount of systemic injury in infected humans. That would explain the apparent progressive de-

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crease of the daily growth rate that has been described worldwide, and which has led to a relatively constant number of new confirmed cases of the Coronavirus Disease 2019 (COVID-19) during the last month (Figure 1). This theoretical speculation is also based on long-term evidence that supports the concept of viral natural and genetic attenuation through mutation of RNA viruses [8, 9]. This concept has been previously proposed as an explanation for the evolutionary behaviour of other RNA viruses, such as the H1N1 influenza A virus. H1N1, in particular, has experienced multiple extinction events during its circulation in the human population [8-11].

In Latin America, a region significantly affected by the COVID-19, a slow but progressive decline in the daily growth rate is noticeable both in countries like Colombia or Chile, which entered a strict quarantine and physical distancing policy early in the epidemic, as well as in Mexico or Brazil, which have had a much more liberal approach (Figure 2) [12-14].

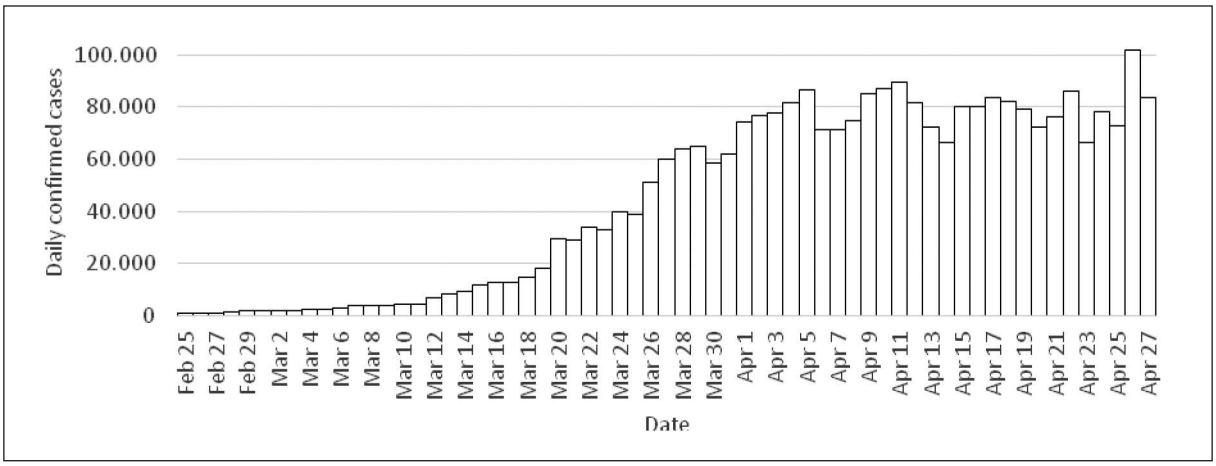

Figure 1 - Number of new daily confirmed cases of COVID-19 worldwide. *Source: Coronavirus Resource Center (1).*

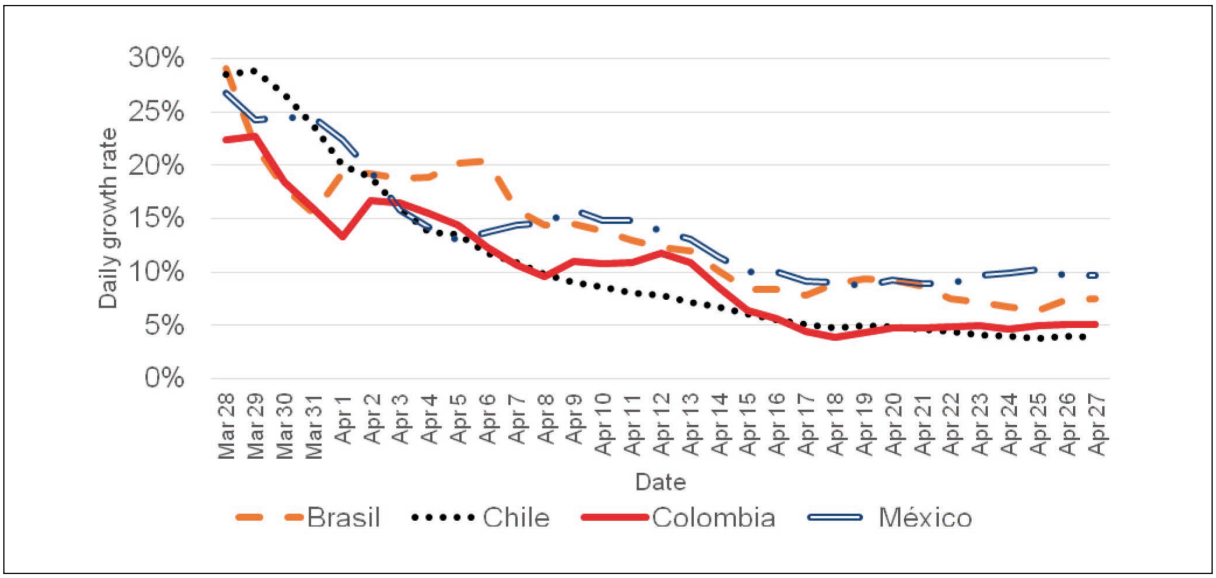

Figure 2 - Daily growth rate (%) of confirmed cases in four Latin American countries during the period March 28 to April 27, 2020.

From an evolutionary perspective, a less aggressive behaviour related mutation could be reproductively successful. The co-existence of different mutations in patients could also perhaps explain the influence of the viral load on the aggressive behaviour observed in some circumstances, as a variety of mutated viruses could include a higher mix of virulent specimens [11, 15].

In conclusion, the reduction of the growth rate of COVID-19 could be explained through deleterious (from the virus perspective) mutations. This would not imply necessarily relaxing epidemic-control strategies but would give a word of hope. While almost every country faces this first COVID-19 wave, options are that the virus drops its lethality over time, and even goes through to temporal extinction periods over the course of years ahead. If we just hold on to current social distancing measures, the problem would just perhaps, go away by itself.

Conflict of interest
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