Emergence and spread of a highly virulent SARS-CoV-2 variant: the tale of the γ variant in the state of São Paulo, Brazil

Abstract

The COVID-19 pandemic had and still have a tremendous impact on all continents, but it has been particularly harsh in South America. The γ SARS-CoV-2 variant that emerged by the end of 2020 in the Brazilian Amazon quickly spread throughout the country reaching all major urban centres thus causing a COVID-19 2nd wave. The γ variant main features were high viral loads and transmission and increased virulence compared to other variants that previously circulated in the country. In the state of São Paulo, the richest and most populous state of Brazil, the toll of the COVID-19 2nd wave surpassed that of the the first eleven months of the pandemic (from March 2020 to January 2021), as 56% of the deaths occurred in the five months of the 2nd wave, between February and June 2021. The already low average age of COVID-19 deaths dropped even further in the pandemic's 2nd wave, declining from an average of 70 to 60 years old; the years of life lost per death per month doubled and the case-fatality rate (CFR) of young adults more than trebled during this period. In addition to describing the impact of the γ variant passage in the state of São Paulo, here we speculate the possible reasons for the emergence and spread of this variant as well as what could have been done to prevent it and minimise its impact. We hypothesise that while the emergence of new variants with increased transmissibility is inevitable, the selection and fixation of variants with increased virulence as the γ lineage could have been prevented. Given the evidence that the emergence and spread of several variants of concern, including γ, resulted from positive selection, we believe that such a highly virulent variant was selected as a response to the selective pressures imposed by the abnormal physical restrictions during the pandemic months. In addition, these restrictions had a negative impact on people's health, which might have contributed to São Paulo's high death toll. Had the γ variant not emerged, the death rate, particularly among young adults, would have been considerably lower even if other variants were allowed to freely circulate in the host population.

Keywords: pandemic, COVID-19, SARS-CoV-2, VOC, γ, mutations, selection

The aetiological agent of COVID-19 – SARS-CoV-2, swept the world over an interval of few months, reaching all countries in all inhabited continents, and causing a global pandemic of high proportions (WHO, 2021). The COVID-19 pandemic reached Brazil by March 2020, causing the 1st wave and resulting in thousands of cases, deaths, lockdowns and other social restrictions. To date (November 2021), more than 600,000 Brazilians perished due to COVID-19 and more than 22 million had confirmed infections (SUS, 2021). In particular, the COVID-19 2nd wave that erupted in December 2020 in the state of Amazonas and soon after that in other parts of Brazil, was particularly devastating. SARS-CoV-2 evolves with a mutation rate of about $3{\times}10^{-6}$ per nucleotide per replication cycle, in line with other coronaviruses (Sender et al., 2021). Such rate translates to ~ 0.5 mutations per infected individual if a maximum limit of 3×10^8 infectious units produced over the course of an infection is assumed (Sender et al., 2021). With this relatively high mutation rate the emergence of many new variants is expected, however, only a few of them confer some significant selective advantage to the virus and effectively increase their share in the population pool. Some of these new variants are of public health concern (known as 'variants of concern' or VOC) either because they have an increased capacity of causing severe illness or because they are more efficiently transmitted than other variants. VOCs are named after the greek alphabet letters – for instance α, β, γ and δ (Choi and Smith, 2021). The α VOC (B.1.1.7) emerged in the United Kingdom (Chaillon and Smith, 2021); β (B.1.351) appeared first in South Africa (Tegally et al., 2021); γ (P.1 or B.1.1.28) emerged in Brazil (Faria et al., 2021) and δ (B.1.617) was first detected in India (India, 2021). All of these four VOCs were first detected between September and December 2020 and carry mutations that are associated with increased transmission and disease severity. Some of them also display higher lethality and immune escape (Choi and Smith, 2021). It should be noted that a variant can be classified as VOC in one country where it is widely circulating while be regarded as a Variant Being Monitored (VBM) in another country where it is circulating at very low levels (CDC, 2021).

The emergence and spread of the γ VOC

The γ VOC was first detected in Manaus by November 2020 (Faria et al., 2021) where it caused in the subsequent months a severe COVID-19 2^{nd} wave with a significant increase in the number of cases and deaths in the Amazonas state (Freitas et al., 2021a). From there, the γ variant disseminated throughout the country with a similar pattern of high lethality. The γ variant harbours a total of 25 mutations (synonymous and non-synonymous) compared with its most closely related ancestral, including 10 amino acid substitutions in the spike protein, some of them associated with a higher degree of transmissibility (Faria et al., 2021, Martin et al., 2021). In addition, the viral load in patients infected with the γ variant was ~10-fold higher than in those with other SARS-CoV-2 variants (Naveca et al., 2021). These features likely contributed to increment the level of virulence (defined as virus-induced host mortality (Regoes et al., 2000)) of this new variant. It has been claimed that part of the devastating effects of the γ variant in Manaus could be ascribed to the already debilitated health care system and unpreparedness of the local health authorities to the new COVID-19 wave (BBC-Brasil, 2021). Nonetheless, the upsurge in cases and deaths was not restricted to Manaus and bordering counties, but rapidly swept through most Brazilian urban centres (Banho et al., 2021, Barbosa et al., 2021, da Silva Francisco Junior et al., 2021, de Oliveira et al., 2021, Freitas et al., 2021b, Martins et al., 2021, Nonaka et al., 2021, Varela et al., 2021). A glimpse of the literature regarding the clinical and epidemiological patterns of the γ variant throughout Brazil reveals similar characteristics. For instance, de Oliveira et al. (2021) reported that young patients aged 20-29 years-old diagnosed in February 2021 in the southern state of Paraná displayed a 3-fold higher risk of death compared to those diagnosed in January 2021. The case-fatality rate (CFR) in this age group went from 0.04% in January (before the arrival of the γ variant) to 0.13% in February, while patients from 30 to 59 years-old showed approximately a doubled CFR. Similarly, in the Rio Grande do Sul state (also in southern Brazil), the proportion of COVID-19 deaths among patients under the age of 60 increased from 18% in November and December to 28% in February (Freitas et al., 2021b). Not only the COVID-19 victims were younger than before, they were also healthier, as the share of patient deaths without pre-existing risk conditions increased from 13% to 22% in the second wave (Freitas et al., 2021b).

COVID-19 2nd wave in the state of São Paulo

The following is a brief description of the epidemiology of the COVID-19 2nd wave in the state of São Paulo, Brazil, which critical phase went from February to June 2021. Similarly to what have occurred in the great Spanish flu pandemic, the COVID-19 2nd wave was considerably harsher than the first one. In the state of São Paulo as in other Brazilian states the γ SARS-CoV-2 variant was remarkably deadlier and more transmissible than the Wuhan and other variants that circulated during the first wave and in the subsequent months prior to the emergence of the γ VOC, particularly towards patients in the 20-59 age group.

From March 2020 to June 2021 (16 months in total) approximately 4 million COVID-19 cases and over 142,000 COVID-19 deaths were registered in the state of São Paulo (Seade, 2021a). Of these, 50.3% of the cases and 56.2% of the deaths occurred during the five months of the 2nd wave between February and June 2021 (Figure 1).

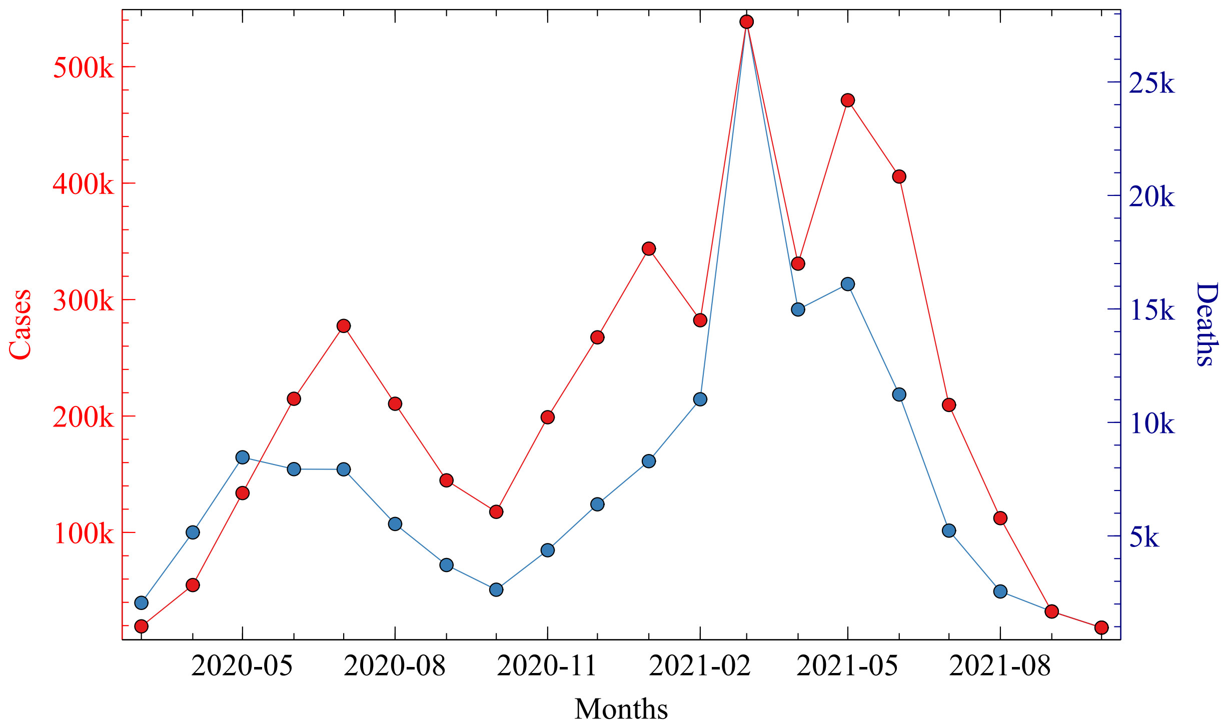

Fig 1. COVID-19 cases (red) and deaths (blue) in the state of São Paulo throughout the pandemic from March 2020 to October 2021. Data was obtained from Seade (2021a) downloaded on 29.11.21.

In line with low- and middle-income countries (Demombynes, 2020, i Arolas et al., 2021), the average age of COVID-19 deaths in São Paulo was below the life expectancy at birth (76.4 years old (Seade, 2020)). Prior to February 2021, the average age of COVID-19 victims in the state was 69.3 years old, hereafter it steadily plunged, reaching 59.4 years old by May 2021 (Figure 2). Accordingly, the average years of life lost per month was 9.63 years/death/month, this number increased to 18 years/death/month at the height of the 2^{nd} wave (Figure 2). Following the retreat of the γ variant (Figure 5), the mean age of COVID-19 deaths went up to 71-72 years old and the years of life lost declined to around 7.5 per death per month. These data demonstrate that the γ VOC not only caused more deaths than the previous variants, but that it was considerably deadlier towards younger people.

COVID-19 CFR oscillated throughout the pandemic (Figure 3). It was artificially

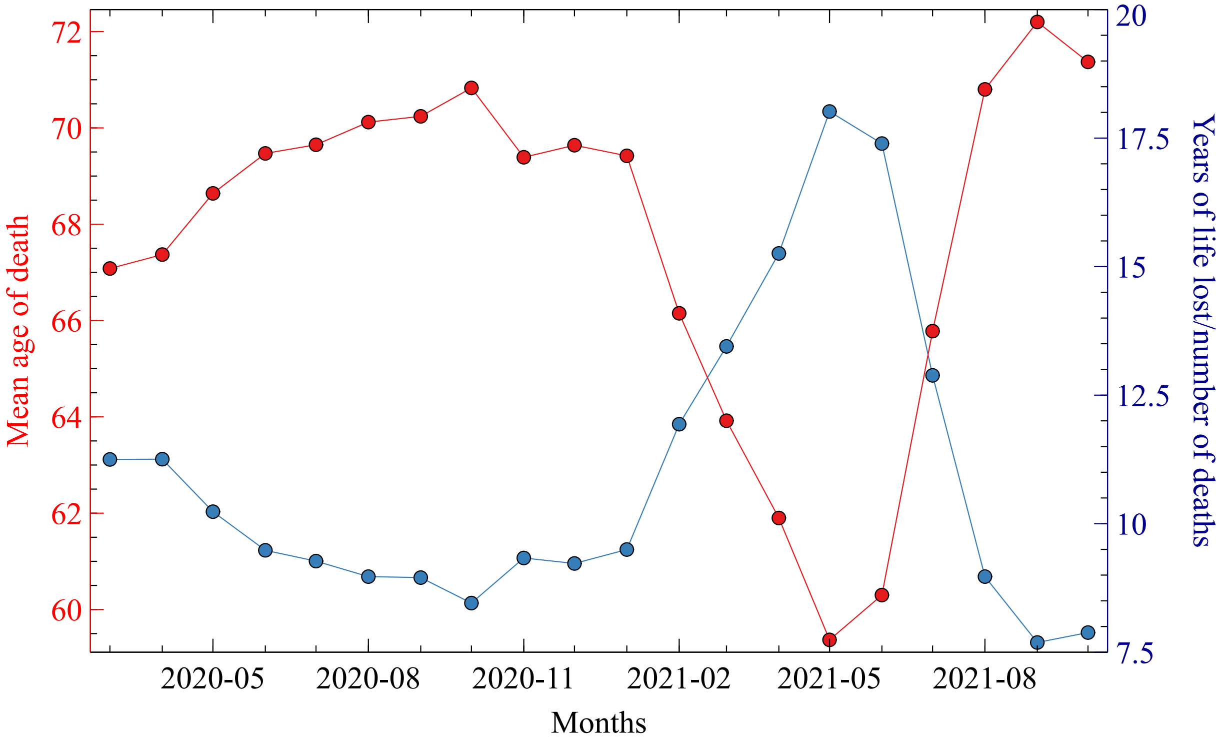

Fig 2. Average age of COVID-19 deaths (red) and years of life lost per number of deaths in each month (blue) throughout the pandemic (March 2020 - October 2021) in the state of São Paulo. Data was downloaded on 29.11.21 from Seade (2021a).

high in the first 3-4 months (March to June 2020) due to the low level of testing (Figure 3). As the number of tests increased, the CFR declined, stabilising at under 3% by July 2020 and maintaining this rate until February 2021, the month that marks the beginning of the steep increase of deaths in the 2^{nd} wave. Henceforth, the CFR increased by more than 2-fold, indicating the spread of the virulent γ variant, as had been previously observed in Manaus (Freitas et al., 2021b). The number of tests was reduced considerably after July, and soon after the government of São Paulo ceased publishing data about testing implementation.

A break by age groups shows that the impact of the γ variant on the CFR was not evenly distributed among the different age categories. While the CFR of the youngest (0-19) and the oldest (60-90+) changed little or not at all in the 2^{nd} wave, the CFR of young adults (20-59 years old) increased 2.6 to 4-fold in this same period (Figure 4).

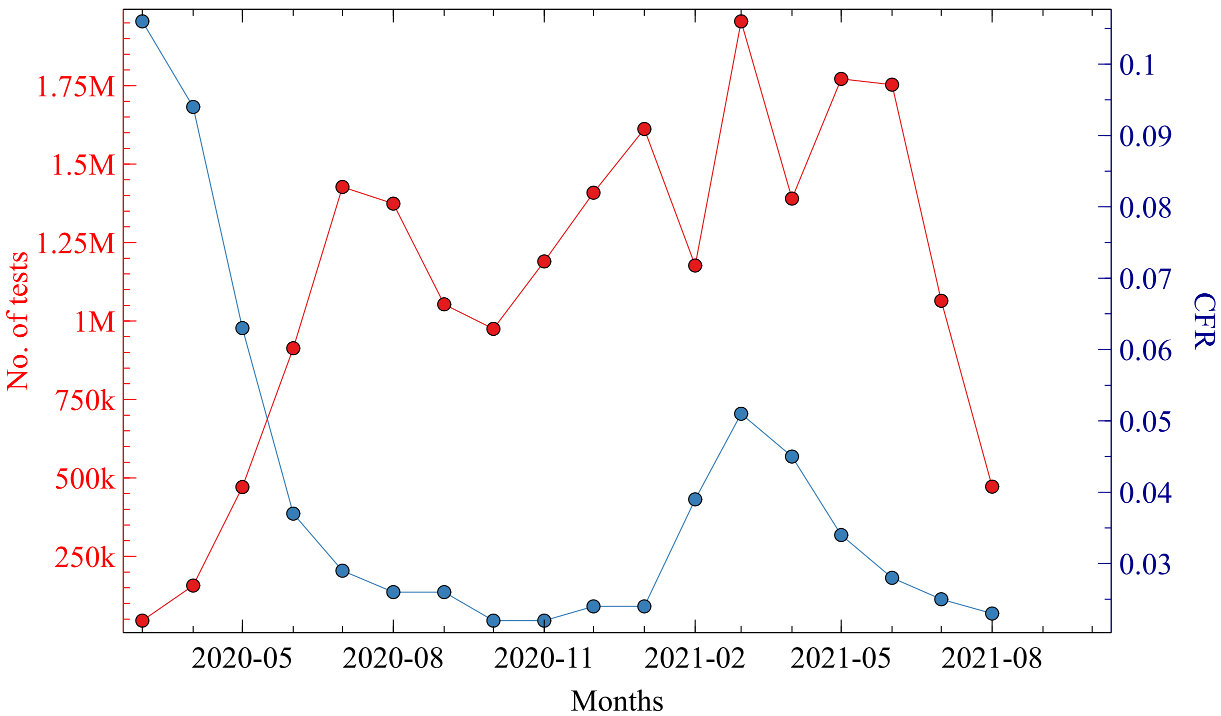

Fig 3. Number of COVID-19 tests per month (red) and the evolution of the CFR (blue) in the state of São Paulo. CFR was calculated from data obtained from Seade (2021a) downloaded on 29.11.21. Testing data from https://www.saopaulo.sp.gov.br/planosp/simi/dados-abertos/

The lack of impact on the mortality of the 60-90+ population could not be ascribed to their vaccination, as the mass vaccination of > 70 years old people began only on 15 March (g1, 2021, Vacinaja, 2021), when the 2nd COVID-19 wave was already ravaging the state (Figure 1). These data indicate that the γ variant was especially deadlier towards young adults.

The new highly virulent γ variant quickly swept the country, such that by May 2021 > 90% of the sequenced genomes in Brazil belonged to the γ lineage (Figure 5). The γ variant predominated in Brazil until the end of July 2021. From then on it was rapidly replaced by the δ variant, by mid September only ~ 4% of all SARS-CoV-2 sequences in Brazil corresponded to γ.

The impact of the γ VOC on young adults

Because young adults were more severely burdened by the COVID-19 2nd wave than the other age tiers, from now on we are going to focus on the 20-39 years old age group. The 20-39 age group represents 32.2% of São Paulo's population. From March 2020 to January 2021, people in this age group constituted 41.4% of the registered COVID-19 cases but only 3.6% of the deaths. In the months that followed (February-June 2021) the share of cases of this age group remained almost unaltered (39.6%), but their proportion in the pool of deaths rose to 7.5%. Accordingly, the CFR of the 20-39 tier climb from 0.2% (July-December 2020 average) to 0.75% (February-June 2021 average), a 3.75-fold increase (Figure 4). Seventy three percent of the deaths in the 20-39 age group occurred in the Feb-Jun 2021 period. In addition, while 68% of the 20-39 years old COVID-19 victims up to January 2021 carried at least one comorbidity, this proportion dropped to 53% in the 2nd wave (Table 1). Thus during this 5-month period the profile of COVID-19 deaths changed considerably, with a shift to younger

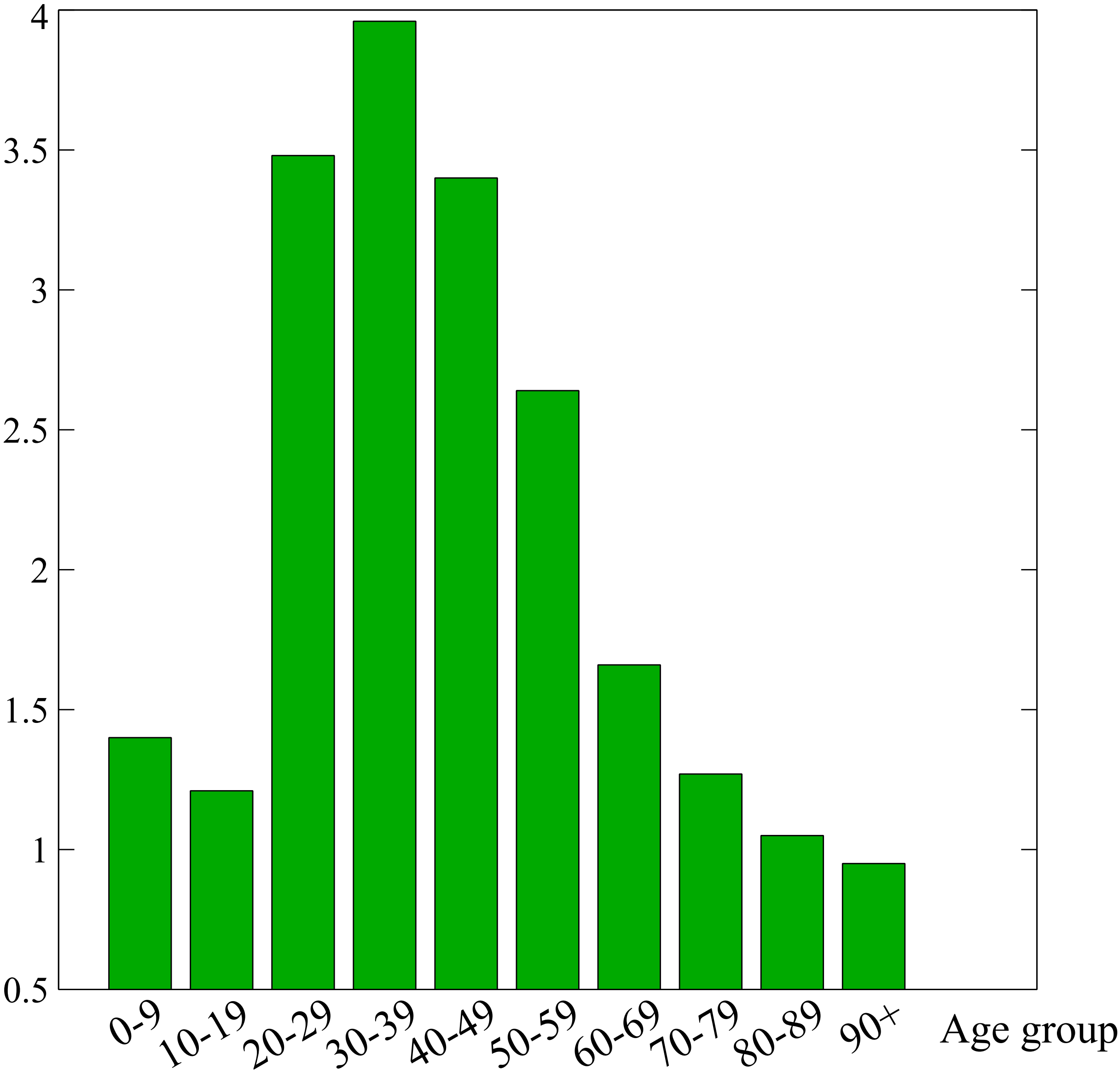

Fig 4. CFR increase in the different age groups in the COVID-19 2nd wave in the state of São Paulo. The mean CFR of each age group in the Feb-Jun 2021 period was divided by the corresponding CFR of each age group in the period Jul-Dec 2020. CFR was calculated from data obtained from Seade (2021a) downloaded on 29.11.21.

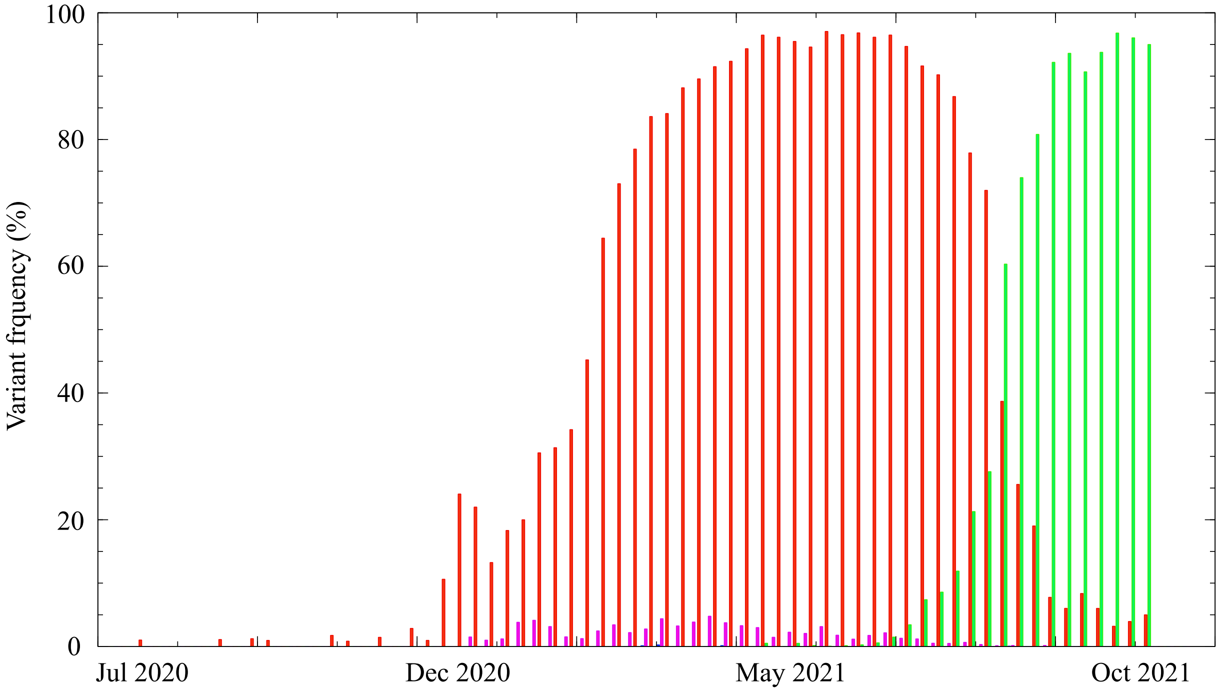

Fig 5. Frequency of SARS-CoV-2 VOCs α, β, γ and δin Brasil (from July 2020 to October 2021). Total number of sequenced VOCs = 59,982; total number of sequenced genomes = 64,378. Red bars, γ; green bars, δ; pink bars, α; blue bars, β. Data downloaded on 31.10.21 from http://www.gisaid.org.

and healthier (with no comorbidities) victims and confirming what has been reported elsewhere regarding the increased virulence of the γ VOC towards young adults (Banho et al., 2021, Barbosa et al., 2021, da Silva Francisco Junior et al., 2021, de Oliveira et al., 2021, Freitas et al., 2021b, Martins et al., 2021, Nonaka et al., 2021, Varela et al., 2021).

Table 1. The impact of COVID-19 on the 20-39 age group in terms of cases and deaths from March 2020 to June 2021. Data downloaded from Seade (2021a) on 29.11.21.

	Cases or Deaths	% of the total
Cases (total)	1615906	-
Deaths (total)	8214	-
Cases (Mar2020 - Jan2021)	820635	50.8[1]
Deaths in (Mar2020 - Jan2021)	2248	27.4[2]
Deaths (Mar2020 - Jan2021) with at least one comorbidity	1533	68.2[3]
Deaths (Mar2020 - Jan2021) with 0 comorbidity	715	31.8[3]
Cases (Feb - Jun 2021)	795271	49.2[1]
Deaths (Feb - Jun 2021)	5966	72.6[2]
Deaths (Feb - Jun 2021) with at least one comorbidity	3151	52.8[4]
Deaths (Feb - Jun 2021) with 0 comorbidity	2815	47.2[4]

[1] relative to the number of total cases
[2] relative to the number of total deaths
[3] relative to the number of deaths in Mar2020 - Jan2021
[4] relative to the number of deaths in Feb - Jun 2021

One possibility is that the augmented mortality observed in the 2nd wave in São Paulo was a product of the chaotic healthcare response to hospital overload. However, while this may have contributed to exacerbate the mortality rate in some cases, the vast majority of deaths were not caused by hospital overload for a couple of reasons. First, even at the peak of the 2nd wave the proportion of used UCI beds in the state of São

Paulo never reached 100% (Seade, 2021b). Second, the CFR did not increase in all age groups (Figure 4) as was expected if the cause of CFR increase was poor healthcare response. We conclude thus that the high level of transmission and mortality observed during the COVID-19 2nd wave was primarily due to the emergence and spread of the highly lethal γ VOC.

Could the selection and spread of the γ variant have been prevented?

Historic experiences with the 1918 Spanish flu and subsequent flu pandemics showed that increased severity in second and later pandemic waves may be the rule rather than the exception (Simonsen et al., 2018). Data from military and civilian populations in the United States, UK, and Australia provide a strong epidemiological evidence of cross protection between the first and second 1918 flu pandemic waves (Barry et al., 2008). It has been estimated that infection with influenza in the 1918 spring (1st wave) provided a 35% - 94% protection against the disease in the fall (2nd wave) and 56% - 89% protection against death (Barry et al., 2008). Similarly, a 61% protective effect by respiratory infection in the Spanish flu 1st wave against mortality in the autumn wave in the Australian army has also been reported (Shanks et al., 2010). Therefore, the benefits of cross-protection during subsequent waves could have been considered before implementing public health interventions designed to limit exposure in the first wave (Barry et al., 2008). This is even more true in the case of COVID-19 that in its first wave targeted mainly older people, which might have been specifically protected, while the rest of the population slowly acquires immunity against the new virus (Akamatsu et al., 2021, Kulldorff et al., 2020).

As shown above, the selection and spread of the γ variant had adverse consequences towards almost all age groups, but its impact was particularly harsh towards young adults (20-39 years old), that have largely been spared during the first wave and in the months before February 2021. In the first 11 months of the COVID-19 epidemic in São Paulo (Mar2020 – Jan2021) there were 2248 COVID-19 deaths in the 20-39 age group, 31.8% of those (715) with no known comorbidity. In the 5 months that followed (Feb-Jun 2021), the number of COVID-19 victims in this age group was 5966, of which 2815 (47.2%) bore no known comorbidity (Table 1). Had the CFR of this age group remained 0.2% (the average CFR before February 2021) throughout the 16 months of the pandemic, the expected number of deaths would have been 3232 ($1,615,906\ cases\ \times\ 0.2\%$) instead of the 8214 registered COVID-19 deaths. Given that the outstanding 3.75 times augment in the CFR in the 2^{nd} wave was caused by the spread of the more virulent γ variant, the prevention of its spread in São Paulo would have spared the lives of 4982 young adults (60.7% of 8214, the total number of deaths in this age group). In fact, the number of deaths would have been even lower had the γ variant not emerged because there would be less cases as well (there were 2.13 times more cases/month in the 5-month 2^{nd} wave than in the previous 11 months). Assuming that the emergence and spread of the γ variant were inevitable, a prior exposure to other SARS-CoV-2 variants might have conferred immunity against the γ variant to the vast majority of the 20-39 age group. This could have been done only by not implementing the physical distancing measures in the state of São Paulo during the first 11 months of the epidemic. The problem with this proposition is that in theory, the lack of physical distance and other restrictions would cause a considerable increase in the number of cases and proportionally an increase in the number of deaths. But, would it? Ultimately, the number of deaths depends on the virus prevalence in a population. The proportion of the population that is susceptible AND potentially symptomatic to COVID-19 remains unknown. It is unlikely that 100% of the population is susceptible for several reasons: (I) as of November 2021, 21 months since the COVID-19 pandemic was declared by the WHO, no country has presented a prevalence (proportion of cases/population) higher than 25% (Owid, 2021), even in countries with small populations, with high levels of testing, or with low physical distancing restriction measures (Hasell et al., 2020). The world mean and median prevalence are 5.1% and 3.7%, respectively, which implies that in most countries SARS-CoV-2 prevalence is below 10%. ; (II) a considerable share of the world population is likely to be naturally immune to COVID-19 as studies have reported that 20% to 50% of people not previously exposed to SARS-CoV-2 displayed T cell reactivity to this virus (Doshi, 2020, Loyal et al., 2021); (III) the disease is asymptomatic in many people, notably in children and teens (Aykac et al., 2021, Szablewski et al., 2020, Zimmermann and Curtis, 2020). Therefore, it is reasonable to argue that the majority of people is either immune or asymptomatic to COVID-19.

The estimation of COVID-19 infection-fatality rate (IFR) is notoriously difficult and attempts have been made to calculate its value with more or less accuracy (Irons and Raftery, 2021, Levin et al., 2020, Luo et al., 2021, Staerk et al., 2021). For instance, Irons and Raftery (2021) estimated that the real number of infected people in a population is likely to be at least twice as high as the official number of cases. However, some reports have claimed that extensive RT-PCR testing, as has been done in several places around the world could be a reliable tool to infer the number of infections in a populations (Luo et al., 2021). An assessment of the COVID-19 prevalence in Manaus in October2020 (before the emergence of the γ variant) based on an extrapolation of seroprevalence data came out with an incredibly low IFR, based on an estimated attack rate of 76% (Buss et al., 2021), a proportion at or close to the herd immunity of Manaus' population. Clearly, this number was an overestimation given the explosion of the COVID-19 2nd wave two months later with twice more deaths than has been previously observed (2889 deaths from 01 Apr to 31 Oct 2020; 5659 deaths from 01 Dec 2020 to 30 Apr 2021 (SUS, 2021)). It has been claimed that the high numbers of cases and deaths in Manaus' 2nd wave could have been caused by reinfections (Sabino et al., 2021), but no concrete evidence was provided in this regard. Other studies have shown that previous COVID-19 infection confers a high degree of immunity (Gazit et al., 2021, Hall et al., 2021) and that reinfections, when they occur, have 90% lower odds of resulting in hospitalization or death than primary infections (Abu-Raddad et al., 2021).

Given the exposed above it is reasonable to assume that the probable maximum share of the population that is susceptible and potentially symptomatic to COVID-19 should be around 20 and 25%, which means that at least 75% of the population is either immune or asymptomatic. Surely this proportion varies among different countries and also among different populations in a single country. We would expect that younger populations, such as that in the 20-39 years old range would have a lower prevalence than older populations. In São Paulo, the fraction of 20-39 years old people with confirmed infections (cases) up to July 2021 was 11.2% (1,615,906 cases in a 14,390,429 population). Assuming that the upper limit of symptomatic infections is 25% of the population the corresponding maximum number of COVID-19 cases would have been 3,597,607. With a CFR of 0.2% (the CFR before the emergence of the γ variant), 7195 deaths would be expected, 1019 less deaths than were actually registered until 30 June 2021. The γ variant was particularly nasty towards patients with no known comorbidity in the 20-39 age group. The CFR in this subgroup increased 6.2 times – from 0.06% before γ emergence to 0.37% in the 2nd wave. With a CFR of 0.06% the maximum number of deaths in this group during the entire pandemic would have been 2159 (0.06% of 3,597,607) instead of the 3,530 registered until the end of June 2021, a 40% reduction.

Additionally, some of the consequences of the physical distancing measures, such as general health deterioration caused by diminished physical activity and weight gain may have contributed to increase the proportion of obese individuals, an important comorbidity that is is associated with increased risk of hospitalization, critical care admission and fatalities, especially in patients under 60 years old (Alberca et al., 2020, Sanchis-Gomar et al., 2020). In fact, it has been reported that during the pandemic the intake of highly caloric ultraprocessed food increased (Ruíz-Roso et al., 2020), which along with a reduction in mobility and physical activities (Stockwell et al., 2021) resulted in heightened levels of obesity during the COVID-19 pandemic (APA, 2021, Lange et al., 2021, Robinson et al., 2021, Woolford et al., 2021). These trends were particularly pronounced among persons with high BMI, which have increased even further during the pandemic (Robinson et al., 2021). Indeed, the risks associated with COVID-19 are greatly enhanced as the patient's BMI increases; a person with a BMI > 40 Kg/m^2 has a significant worse prognosis than one with a BMI of about 30 Kg/m^2 (Cava et al., 2021). As a result, a non-negligible fraction of young adults that perished in the pandemic 2nd wave may have acquired an extra vulnerability caused by weight gain during the first year of the pandemic that have likely contributed to their deaths.

The restrictions imposed since the beginning of the pandemic might have affected people's resilience against the γ variant through other ways as well: (1) by preventing or diminishing immunity to the γ variant which might otherwise have been acquired through exposure to other coronaviruses or to less lethal SARS-CoV-2 variants. It is believed that the low COVID-19 death rate in Japan and other Pacific Rim countries could be at least partially ascribed to previous exposure to other coronaviruses which might confer cross protection against SARS-CoV-2 (Chiu et al., 2021, Dijkstra et al., 2021, Shrock et al., 2020, Yaqinuddin, 2020); (2) Lockdowns, curfews and the move to home-based work prevented direct exposure to sunlight, which is necessary for the biosynthesis of Vitamin D from 7-dehydrocholesterol. Though the evidence in favour of vitamin D role in COVID-19 prevention and treatment is still inconclusive (Vimaleswaran et al., 2021), it has been shown that patients with severe vitamin D deficiency have higher degree of hospitalisation and mortality risk (Carpagnano et al., 2020, Pereira et al., 2020). Thus less exposure to sunlight due to mobility restrictions may have caused a reduction in vitamin D serum concentration, which in turn contributed to a severe outcome in some patients; (3) by limiting, disrupting or halting physical activity. It is known that physical exercises act as modulators of the immune system (da Silveira et al., 2020) and that moderate-intensity exercises are “immunoenhancing” (Laddu et al., 2021, Simpson et al., 2015). The mobility restrictions, the move to home-based work and the forced closing of gyms have all contributed to a general decrease in physical activity which might have otherwise helped combating respiratory infections such as COVID-19.

Could the emergence of VOCs have been predicted?

With a mutation rate of $\sim 3 \times 10^{-6}$/nt/replication cycle (~0.5 mutation per infection and an evolutionary rate of ~ 3 mutations per month) (Sender et al., 2021) the emergence and selection of variants with increased power of transmission was inevitable. The more important question is whether the emergence of more virulent variants that would incur more damage on hosts than the previous ones could have been predicted. The answer to this question is less clear. On the one hand, high number of cycles of virus replication, as ensued during a pandemic, can speed viral evolution simply by increasing genomic diversity and the chances of acquiring beneficial mutations. From this perspective, the most effective strategy to prevent the emergence of new and more virulent variants is by limiting the number of infections in the susceptible population as much as possible (Boni et al., 2013). Also, high levels of infection can increase the probability of coinfections, which may foment, through recombination and reassortment, the emergence of new and more virulent strains (Shapshak et al., 2011, Simon-Loriere and Holmes, 2011). However, there is currently no evidence that the COVID-19 γ variant evolved through recombination events. In fact, the γ lineage, first detected in November 2020, harbours a total of 25 mutations (synonymous and non-synonymous) compared to its closest ancestral (isolated in March 2020) (Faria et al., 2021). Because SARS-CoV-2 evolves at a rate of 3 mutations per month (Sender et al., 2021), there was ample time for the γ variant to acquire the relevant mutations without resorting to recombination.

It is generally believed that the rate of pathogen transmission and virulence are positively associated with the degree in which the pathogen exploits its host and that both virulence and transmission rates are enhanced by within-host high replication rates (Day, 2003, de Roode et al., 2008, Mackinnon and Read, 1999). For instance, in Influenza both transmission and virulence are affected by mutations that result in increased rates of pathogen replication in the host (de Jong et al., 2006). Likewise, most studies have shown a direct association between SARS-CoV-2 viral load, disease severity and mortality (Kawasuji et al., 2021, Knudtzen et al., 2021, Makov-Assif et al., 2021, Rabaan et al., 2021, Shenoy, 2021, SINGH et al., 2021, Wright et al., 2021). Higher viral loads enhance the rate of contagion as more virus particles are available to be transmitted by shedding or through other mechanisms. The notion that a high viral nasopharyngeal load increases viral transmission is indeed quite intuitive and was, in fact, confirmed by the data (Bjorkman et al., 2021, He et al., 2020, Kawasuji et al., 2020, Marks et al., 2021, Yang et al., 2021). Thus mutants that produce high viral loads in infected tissues, in particular in the host's upper respiratory tract have a selective advantage over competitors during the course of an epidemic. The selection of high-viral-load mutants is likely to be stronger under conditions that hinder free viral transmission such as abnormal physical distancing among the host population during an epidemic. In this case, variants that produce high viral loads would also be the ones with the highest ability of transmission and with the highest probability of fixation even at the cost of reducing the life span of the host. Though this hypothesis cannot be directly tested, there is now strong evidence that positive selection has played a pivotal role in the emergence and spread of the α, β andγ VOCs (González-Candelas et al., 2021, Martin et al., 2021). At least five convergent mutations emerged in those fast-spreading lineages where each of them, either alone or in combination, provide some significant fitness advantage(Martin et al., 2021). Since natural selection occurs as a response to a selective pressure, we propose that the unnatural restrictions imposed on the host population provided the necessary selective pressure that eventually selected the γ variant. Conversely, under conditions of exponential growth in a population of naive susceptible hosts there is not significant selective pressure on the pathogen, and a slow mutational pattern guided by random genetic drift is expected (MacLean et al., 2021). In other words, had the virus been allowed to spread as if during normal flu/cold seasons, new SARS-CoV-2 variants with increased levels of virulence may have not been selected. Another piece of evidence came from the study of bacteriophages (Berngruber et al., 2013, Bull, 2006). Once a viral pathogen with high virulence emerges at the beginning of the epidemic (when prevalence is still low), it quickly spreads through the host population and wins the competition against less virulent variants. As the pathogen prevalence increases, the selection on virulence is reversed favouring the spread of more benign pathogens. Accordingly, judging by the high number of infections in the 2nd wave compared to the first one, the prevalence of SARS-CoV-2 in the host population was still relatively low before the emergence of the γ variant. In turn, by August 2021 γ was displaced by the δ variant (Figure 5), a highly transmissible but less virulent VOC (Earnest et al., 2021, Edward et al., 2021), corroborating the hypothesis of reversed virulence once the prevalence in the population was sufficiently high.

In conclusion,...

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