
Impact of SARS-CoV-2 variants on modulating COVID-19 case and death curves in Brazil.

Impacto das variantes do SARS-CoV-2 na modulação das curvas de casos e óbitos da COVID-19 no Brasil

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RESUMO

Ainda que compartilhe de uma alta similaridade genética aos coronavírus antecessores, o SARS-CoV-2 apresenta maior facilidade de transmissão, principalmente através de aerossóis, contato com indivíduos infectados e superfícies contaminadas. Os coronavírus apresentam uma taxa elevada de mutações por unidade infecciosa produzida, resultando no aparecimento de diferentes variantes e linhagens, representando um importante desafio, podendo apresentar um potencial de gravidade muito maior que a cepa original. Ao longo do presente estudo, foi possível observar um aumento na média de casos entre os anos de 2020 e 2021, seguida de uma redução dos casos no ano de 2022 em relação a 2021, que pode ter sido originada pelo aumento da taxa de vacinação entre 2021 e 2022. Cabe ressaltar que houve um forte movimento anti-vacina, afetando o esquema vacinal da população e interferindo na associação entre casos e óbitos e as doses da vacina, além de estimular a seleção de cepas capazes de reduzir a eficácia dos imunizantes distribuídos. Ainda que haja limitações referentes à subnotificação, pode-se concluir que o esquema vacinal estipulado pelo Ministério da Saúde foi eficaz no controle da pandemia no Brasil, ao passo que as variantes estão diretamente relacionadas à modulação das curvas da doença.

Palavras-chave: COVID-19; SARS-CoV-2; Vacinação; Variantes.

ABSTRACT

Even though it shares a high genetic similarity to its predecessor, SARS-CoV-2 is more easily transmitted, mainly through aerosols, contact with infected individuals, and contaminated surfaces. Coronaviruses show a high rate of mutations per infectious unit produced, resulting in the emergence of different variants and lineages, potentially having a much greater severity than the original strain. The present study observed an increase in the average number of cases between 2020 and 2021, followed by a reduction in cases in 2022 compared to 2021, which may have been caused by the increase in the vaccination rate between 2021 and 2022. There was a strong anti-vaccine movement, affecting the population's vaccination schedule and interfering in the association between cases, deaths, and vaccine doses, stimulating the selection of strains capable of reducing the effectiveness of the vaccines distributed. There are limitations regarding underreporting, however, it can be concluded that the vaccination schedule stipulated by the Ministry of Health of Brazil effectively controlled the pandemic in Brazil, while the variants are directly related to the modulation of the disease curves.

Keywords: COVID-19; SARS-CoV-2; Vaccination; Variants.

INTRODUÇÃO

Coronaviruses are commonly associated with infections in animals and humans, which makes their origin mostly zoonotic (LAMERS; HAAGMANS, 2022). In recent years, some viruses belonging to the *Coronaviridae* family, such as SARS-CoV and MERS-CoV, cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively, were found infecting the upper respiratory tract of humans, mainly causing symptoms associated with a cold. Common (YESUDHAS et al, 2021; LAMERS; HAAGMANS, 2022). In December 2019, an outbreak of acute pneumonia spread across China, responsible for an unknown respiratory syndrome, which was later identified and named as SARS-CoV-2, an enveloped, single-stranded RNA virus whose main target of infection continues to be the respiratory tract, being the causative agent of the so-called COVID-19 (Coronavirus disease 2019) (CHEN, G. et al, 2020; LU et al, 2020; ANVISA, 2021; YESUDHAS et al, 2021).

Although it shares a high genetic similarity to its predecessor coronaviruses, SARS-CoV-2 is more easily transmitted, mainly through aerosols, contact with infected individuals, and even contaminated surfaces (ANVISA, 2021). Given this high transmissibility, in March 2020, the World Health Organization (WHO) declared a pandemic state, presenting outbreaks of COVID-19 cases around the world, in addition to a fatality rate of 2%, becoming the focus of global research (OPAS/WHO, 2020; CORONAVIRUS BRASIL, 2022). Ever since, the disease has had more than 693 million

cases and 6.9 million deaths worldwide (OUR WORLD IN DATA, 2022). After the sequencing of the genetic material of SARS-CoV-2, which took place in January 2020, an accelerated search for vaccines began. In December 2020, with the encouragement of the WHO, nine vaccines against COVID-19 in the world, using different technologies, from the most conventional, with inactivated virus, to more modern vaccines, using viral messenger RNA (OPAS/WHO, 2022).

Coronaviruses present a rate of 105 to 108 mutations per infectious unit produced, given their transmissibility and RNA as genetic material, which has resulted in the emergence of different variants and lineages throughout the pandemic, representing an important challenge, since These variants may have a much greater potential for severity than the original strain (CHEN, J., et al, 2020; ANVISA, 2021; WHO, 2022). Of the entire established classification, variants of concern (VOC) present a risk to global health, an increase in transmissibility or virulence, changes in the clinical course of the disease, and even a decrease in the effectiveness of the protective measures adopted, such as vaccines, therefore being the biggest focus of research (KONINGS et al, 2021; WHO, 2022). In this context, to prioritize global research during the pandemic and assist in controlling the pandemic state, the WHO established a partnership with research institutions and national authorities, in January 2020 to monitor COVID-19 around the world (WHO, 2022).

Regarding the SARS-CoV-2, the Alpha, Beta, Gamma, Delta, and Ômicron variants gained prominence on the world stage and were quickly classified as VOC. Of these, Ômicron has remained predominant since its emergence in November 2021 (KONINGS et al, 2021; REDE GENÔMICA FIOCRUZ, 2022; WHO, 2022). However, even though vaccination is highly effective, its implementation can lead to one of the biggest concerns regarding the pandemic state, which is the emergence of new variants (CHEN, J., et al, 2020; KORBER et al, 2020; CHAKRABORTY et al, 2021; SARINHO et al, 2021), which can lead to a more serious form of the disease and/or difficult laboratory diagnosis by identifying the virus (ANVISA, 2021; WHO, 2022). Therefore, this study, arising from a master's thesis, aims to evaluate the effect of the emergence of new variants of SARS-CoV-2 on the modulation of cases and deaths from COVID-19 in Brazil.

METHODOLOGY

- **Study area and time frame**

An exploratory analysis based on the entire national territory was developed based on secondary data from COVID-19, with a selected time frame from January 2020 to December 2022, corresponding to the critical pandemic period in Brazil.

- **Data analysis**

For the analyses referring to cases and deaths, the data were obtained from the Data Science Platform applied to Health, referring to the Monitora COVID-19 Project – FIOCRUZ (FIOCRUZ, 2020), from the Institute of Scientific and Technological Communication and Information in Health (ICICT-Fiocruz), available at <https://bigdata-covid19.icict.fiocruz.br/>. Given the emergence of variants of concern across the country, data relating to viral genomes were obtained from the Fiocruz Genomic Network, accessible at <http://www.genomahcov.fiocruz.br/>. As these are variants that emerged at the beginning of the pandemic, the alpha and beta variants were grouped in the “Others” category, thus highlighting the most relevant variants for the epidemiological scenario in Brazil. To facilitate data analysis, all variables were grouped monthly.

Data were expressed as mean or median \pm standard deviation (SD), depending on the normality of the results, which was verified using the Shapiro-Wilk test. Statistical analysis of the data was performed using one-way Analysis of Variance (ANOVA) followed by the Tukey test, when normality was characterized as normal, and the Kruskal-Wallis’s test, followed by Dunn's multiple comparison when normality was classified as not normal.

The significance level was defined as ≤ 0.05 . The correlation analysis, between data on cases, deaths, cases by variants, and vaccination doses in 2021 and 2022, was carried out using the Pearson or Spearman tests (depending on normality). The strength of the correlation was defined according to Fávero and Belfiore (2015). Statistical analyses were performed using R software version 3.5.2, while graphs were plotted using GraphPad Prism software.

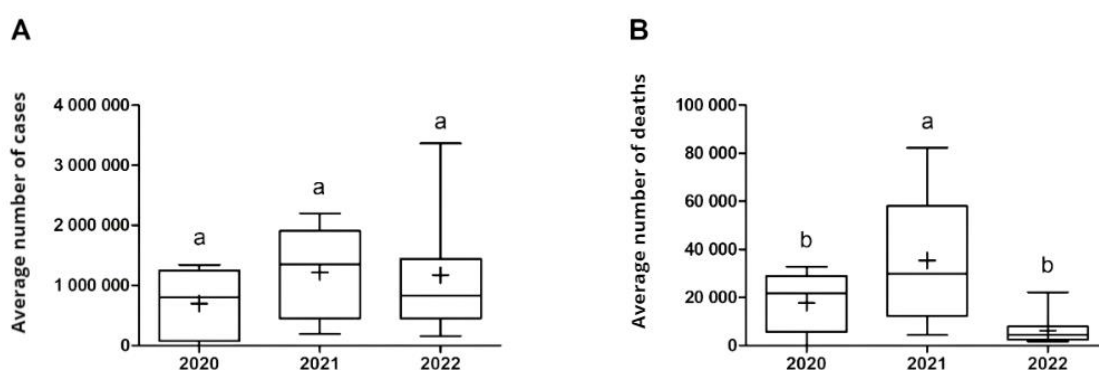
- **Research Ethics Committee**

As the research is based on publicly available database records and does not disclose personal information from participating institutions, submission to the Research Ethics Committee/Committee was not necessary.

RESULTS AND DISCUSSION

The first case of COVID-19 in Brazil was registered in February 2020. The first wave of which began the following month, given the entry of the original strain of SARS-CoV-2. However, in October 2020, the first variants of concern, known as Alpha and Beta variants, were reported (DUONG, 2021; REDE GENÔMICA FIOCRUZ, 2022). Compared to the genome of the original virus, discovered in Wuhan, the new strains accumulated mutations in the spike protein, responsible for the interaction of the virus with the host cell receptor, increasing their transmissibility, virulence and resistance to neutralizing antibodies (MICHELON, 2021). The high mutation rate of SARS-CoV-2 not only favored the adaptability of the virus, but also increased its transmissibility, enabling the occurrence of more serious cases and even deaths, in addition to reducing the effectiveness of vaccines (KORBER et al., 2020; CHAKRABORTY et al., 2021). Figure 1 presents the average data on cases (A) and deaths (B) in the years 2020, 2021 and 2022, where it is possible to observe an increase in the average number of cases between the years 2020 and 2021, followed by a reduction in cases in the year 2022 when compared to 2021.

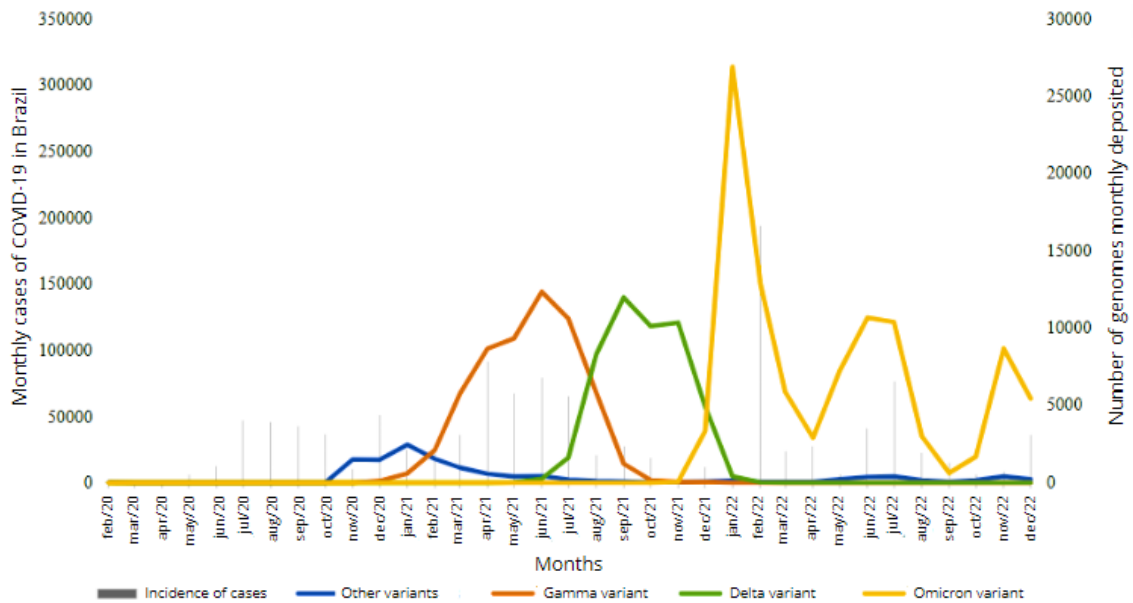
Figure 1 – COVID-19 cases and deaths in Brazil between 2020 and 2022.



Caption: A) average number of cases and (B) average number of deaths in the years 2020, 2021 and 2022 in Brazilian territory. The error bar represents the minimum and maximum values for each year. + represents the average for each year. Letters that are the same above in the boxplots represent the absence of a significant difference, while different letters represent a statistically significant difference between the means for each year (ANOVA ≤ 0.05). Source: The authors (2023).

This reduction may have been caused by the increase in the vaccination rate observed between 2021 and 2022 (Figure 2). However, no statistically significant differences were identified between the changes in cases in these years. Even so, it is possible to see that the Gamma and Ômicron variants proved to be even more transmissible than the previous strains, since, after the emergence of the Gamma variant, in November 2020, there was a substantial increase in cases, forming, therefore, the second wave of the disease in Brazil.

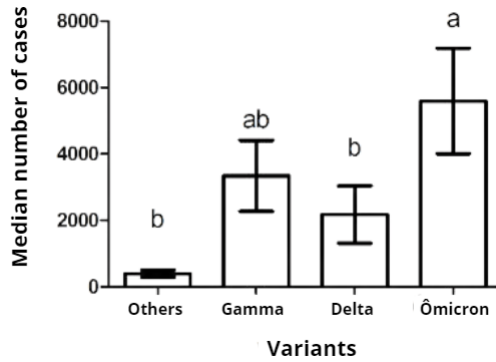
Figure 2 – Comparison between the number of cases and the SARS-CoV-2 variants in Brazil.



Source: The authors (2022)

The lack of statistical difference in the number of cases between the years 2020, 2021, and 2022 may have been influenced by the emergence of the omicron variant in 2022, which kept the number of cases high, being the most dominant variant throughout the pandemic (Figure 3). Therefore, the third wave of the disease is directly related to the emergence of this variant, which is responsible for many cases identified between November 2021 and December 2022, being the most transmissible of the variants of concern reported by the WHO.

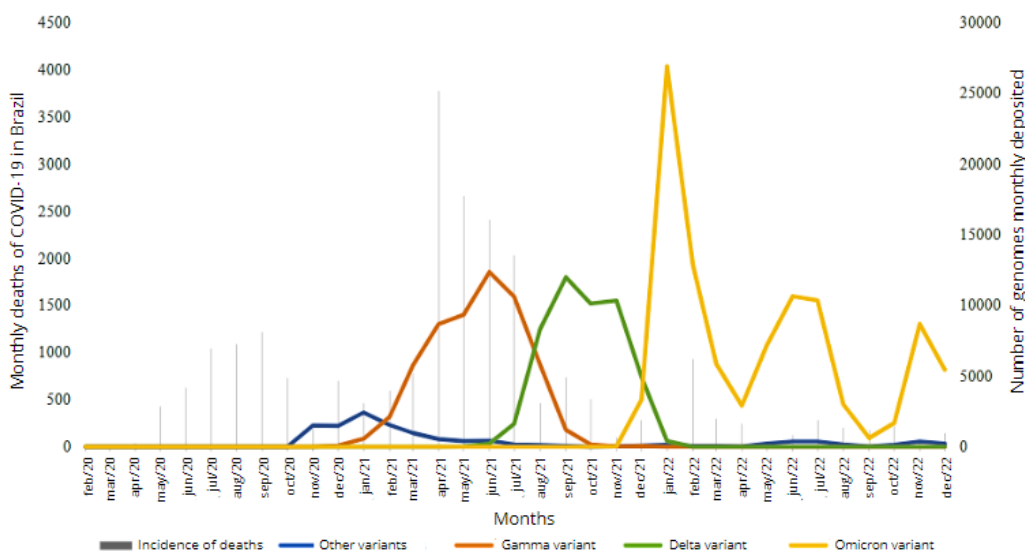
Figure 3 - Median cases per variant during the years 2020, 2021 and 2022 in Brazilian territory.



Legend: The error bar in the columns represents the standard error of the samples. Equal letters above the columns represent no significant difference, while different letters represent a statistically significant difference between the medians of each variant (Kruskal-Wallis ≤ 0.05). Source: The authors (2023).

While the original strain of SARS-CoV-2 totaled almost 160 thousand deaths in the first wave of the disease in the national territory alone, the first notification of which was recorded in March 2020, until the end of the pandemic was declared, COVID-19 reached the mark of 705 thousand deaths (CORONAVÍRUS BRASIL, 2023). On the other hand, there was a significant increase in the average number of deaths between 2020 and 2021 (Figure 1B), most likely associated with the emergence and increase in circulation of the delta and gamma variants, followed by a significant reduction in the average number of deaths in 2022. In this case, the Gamma variant proved to be more lethal, there was a significant increase in the incidence of deaths during the second wave of the disease, as shown in Figure 4.

Figure 4 – Comparison between the number of deaths and the SARS-CoV-2 variants in Brazil.



Source: The authors (2022)

The observed data show a possible positive effect of population vaccination in Brazilian territory, with a 65 and 82% reduction in the number of deaths in 2022, compared to the years 2020 and 2021, respectively. However, the emergence of more adapted strains may also be associated with selective pressure caused by mass vaccination of the population, where it is possible to highlight cases of reinfection after the circulation of the Ômicron variant in Brazil, being able to escape the neutralizing antibodies produced by vaccines and infect previously immunized individuals (COLLIE et al., 2021).

In total, around five vaccines against COVID-19 have been approved, made available and administered throughout Brazil, whose vaccination schedule is stipulated in two initial doses and three booster doses, including Pfizer's bivalent vaccine, which protects against the strains BA.1., BA.4. and BA.5. of the Ômicron variant, ensuring greater protection against SARS-CoV-2 (ANVISA, 2023; MINISTÉRIO DA SAÚDE, 2023a). However, when comparing the emergence of variants with the vaccination period in Brazil, the possibility that vaccination is responsible for the selection of the Delta variant stands out, as it emerged after the two-dose vaccination schedule, being detected for the first time, in June 2021.

It is noteworthy that cases of COVID-19 related to the Gamma variant only decreased after the second dose of the vaccine, where, soon after, the Delta variant appeared, which made it possible to identify suppression of the curve of cases related to this variant after the implementation of the first vaccine booster dose. Furthermore, the Ômicron variant presented increasingly transmissible subvariants, which remained in circulation even with the advancement of booster doses, culminating in new waves of COVID-19 in Brazil until more than 50% of the population was vaccinated with the bivalent booster.

The transmissibility of SARS-CoV-2 increased as the omicron variant advanced, whose mutations gave rise to strains such as XBB.1.5 and EG5., popularly known as Kraken and Éris (OMS, 2022; CNN BRASIL, 2023; G1, 2023), a reduction in lethality was noted. viral, which can be considered an adaptation strategy, since such microorganisms are dependent on the host to replicate and, consequently, infect other individuals (KANTOR et al., 2021).

Pearson's correlation analysis initially showed a strong positive association between the number of cases and deaths in 2021 ($\rho^2 = 0.93$; $p \leq 0.05$) and 2022 ($\rho^2 = 0.90$;

$p \leq 0.05$), which reflects the 3% mortality rate observed in 2020 and 2021, 1% in 2022. A moderate to strong positive association between the gamma variant and the number of cases ($\rho^2 = 0.73$; $p \leq 0, 05$) and deaths ($\rho^2 = 0.76$; $p \leq 0.05$) in 2021 (Table 1), showing that the increased circulation of this variant led to an increase in the number of cases and deaths. On the other hand, a negative association was observed between the delta variant and the number of cases ($\rho^2 = -0.84$; $p \leq 0.05$) and deaths ($\rho^2 = -0.74$; $p \leq 0.05$) in the year 2021, indicating that the increased circulation of this variant would be reducing the number of cases and deaths in Brazilian territory.

Table 1 – Pearson correlation with variants, cases, deaths and vaccine doses applied in 2021 and 2022.

	Other variants	Gamma variant	Delta variant	Ômicron variant	Cases	Deaths	1 st dose	2 nd dose / single dose	3 rd dose / 1 st booster
2021									
Other variants	1,00								
Gamma variant	-0,15	1,00							
Delta variant	-0,60*	-0,57	1,00						
Ômicron variant	-0,21	-0,32	0,07	1,00					
Cases	0,46	0,73*	-0,84*	-0,45	1,00				
Deaths	0,22	0,76*	-0,74*	-0,39	0,93*	1,00			
1 st dose	-0,40	0,78*	-0,04	-0,35	0,33	0,34	1,00		
2 nd dose / single dose	-0,72*	-0,26	0,90*	-0,08	-0,66*	-0,49	0,23	1,00	
3 rd dose / 1 st booster	-0,44	-0,63*	0,56	0,66*	-0,81*	-0,69*	-0,53	0,33	1,00
2022									
Other variants	1,00								
Gamma variant	0,12	1,00							
Delta variant	-0,75*	0,23	1,00						
Ômicron variant	0,38	0,79*	0,10	1,00					
Cases	0,07	0,81*	0,15	0,83*	1,00				
Deaths	-0,19	0,62*	0,27	0,58*	0,90*	1,00			
1 st dose	-0,61*	0,22	0,62*	0,34	0,50	0,59*	1,00		
2 nd dose / single dose	-0,21	0,48	0,42	0,69*	0,71*	0,69*	0,78*	1,00	
3 rd dose / 1 st booster	-0,15	0,57	0,33	0,67*	0,87*	0,91*	0,72*	0,80*	1,00

Source: The authors (2023).

However, considering the start of vaccination in 2021, this negative association may be affected by this fact, as a negative association was observed between the number of cases and deaths and vaccination doses this year, that is, the increase in the rate of vaccination significantly reduced the number of cases and deaths in 2021. In 2022, a strong positive correlation was observed between the gamma and omicron variants with the number of cases and deaths, showing that even after the vaccination began, both

variants were still very infectious and lethal. Otherwise, it is important to note the moderate to strong negative association between vaccination doses and the other variants (alpha and beta), showing a significant reduction in the circulation of these variants after vaccination.

In addition, it was observed a positive association in 2022, between cases and deaths and doses 2 and 3 of vaccination, suggesting that vaccination of the 2nd and 3rd doses would increase the number of cases and deaths. However, it is worth noting that during this period there was a strong anti-vaccine movement, causing the population's vaccination schedule to be affected, which interfered with this association between cases and deaths and doses 2 and 3 of vaccination, in addition to stimulating selection of strains capable of reducing the effectiveness of the vaccines distributed (STOWE et al., 2021; VASILEIOU et al., 2021; OLIVEIRA, 2022). According to the study by Frias and collaborators (2021), more than 80% of deaths from COVID-19 were in non-immunized patients or those who were still within the immunological seroconversion window, that did not yet have antibodies produced against SARS-CoV-2.

There were many challenges regarding the conditions for combating the pandemic, demanding a constant transformation in the State's actions and the strengthening of the Unified Health System (SHIMIZU et al., 2021). Finally, even though there are limitations regarding the underreporting of cases, deaths and genomes deposited, it can be concluded that the vaccination schedule stipulated by the Ministry of Health, containing two initial doses and, to date, three booster doses (MINISTÉRIO DA SAÚDE, 2023b), including the bivalent vaccine, was effective in controlling the COVID-19 pandemic in Brazil, while the variants are directly related to the modulation of the disease's case and death curves.

FINAL CONSIDERATIONS

Even though global public health has constant scientific and technological advances, the humanitarian crisis created by COVID-19 has affected different areas of society. The adaptive capacity of SARS-CoV-2 and the emergence of variants of concern not only generated waves of the disease around the world but also triggered massive investment in the production of immunization agents. Based on this study results, despite favoring the selection of mutant strains of the virus, vaccines against COVID-19 were able to stop the spread of SARS-CoV-2 and modulate the disease rates in Brazil, reducing

the incidence of mild, moderate, or severe cases, the number of hospitalized patients and, mainly, the incidence of daily deaths, even when previously immunized individuals presented new viral strains. Cases of COVID-19 continue to be reported around the world, as new variants of the virus continue to emerge. It is believed that SARS-CoV-2, given its adaptability, may have a unique ability to remain circulating, causing cases of flu-like syndromes as occurs with Influenza, becoming a seasonal virus and present in national vaccination tables.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this article.

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