Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

pose. In this context, specimens from male and female patients with a suspected diagnosis of a STI from April 2019 to March 2021 were analyzed using a commercial real-time PCR assay for detection of mutations associated with azithromycin and moxifloxacin resistance, in order to determine the resistance rates for these antimicrobials and their evolution throughout the study period.

A total of 142/3633 (3.9%) patients who tested positive for MG were included in the study. The first sample from the first episode was taken for each patient. The assay used to diagnose the MG infection was the RT-PCR Allplex™ STI Essential Assay (Seegene®, Seoul, South Korea). Specimens positive in this assay were subsequently tested by the RT-PCR Allplex™ MG & MoxiR Assay (Seegene®) and RT-PCR Allplex™ MG & AziR Assay (Seegene®) for azithromycin, as well as moxifloxacin resistance-associated mutations. The biological specimens were endocervical and urethral swabs that were transported in DeltaSwabs Amies (Deltalab S.L., Barcelona, Spain) and first-void urine samples in a sterile sample container.

MG was detected in 76 (53.5%) male and 66 (46.5%) female patients. Resistance-associated mutations against macrolides were detected in 39/142 (27.46%) strains and against fluoroquinolones in 14/142 (9.86%) strains. The median age was 29 (IQR 25–37.25; 17–58) years, and the prevalence was significantly higher in male patients (44.7% vs. 13.2%, $p = 0.049$).

The percentage of SNPs detected in the 23S rRNA was 26.1% in 2019 and 30% in 2020, while the percentage of SNPs detected in the *parC* gene was 12% in 2019 and 6% in 2020. Detailed information about these detected mutations by year is shown in Fig. 1.

Throughout the study period, we found a slight increase of 3.9% in the resistance rate to azithromycin. The prevalence of mutations associated with fluoroquinolone resistance alone decreased from 12% in 2019 to 6% in 2020. Both evolutions between these 2 years, were not statistically significant.

The most frequent SNP detected was A2059G (37.7%), while A2058G (28.3%) was in second position.[5] Dual mutations conferring resistance to both antimicrobials were found in a total of nine (17%) mutant strains: four A2059G/G248T, three A2058G/G259T and two A2059G/G248A. The presence of dual mutations could increase treatment failure, which was similarly concluded in a study where patients were followed up closely to observe the implication of the presence of dual markers after monotherapy.[6]

Treatment failure in MG infection is associated with recurrent or persistent NGU.[7] Commercial PCR assays for the detection of these mutations allow for the resistance-guided treatment of MG infections, improving cure rates and preventing the spread of resistant strains. Furthermore, the fact that the study can be made with the same DNA extraction is an advantage over other commercial assays.

The main limitations of this study were the lack of a complete clinical history and the number of patients lost to follow-up, which would allow for an analysis of antibiotic failure. However, there is enough data available to support that the presence of these mutations causes treatment failure.[3,7,8]

Finally, the high macrolide resistance rates and the increase of resistance-associated mutations during the study period and, in addition, the established fluoroquinolone resistance rate, which was similar to that from other studies, supports the necessity of analyzing the presence of mutations to perform targeted treatment.

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Case-fatality rates and risk of death from COVID-19 and influenza A/H3N2 in Brazil: A nationwide ecological study

Tasas de letalidad y riesgo de muerte por COVID-19 e influenza A/H3N2 en Brasil: un estudio ecológico a nivel nacional

Brazil is one of the countries with the highest incidence and mortality rates from COVID-19 worldwide. In 2022, the country faced a third wave of the disease associated with community transmission of the Omicron variant. During the first 10 epidemiological weeks (January 2–March 12, 2022), 7,058,717 cases and 35,840 deaths from COVID-19 were recorded. In addition, Brazil has faced an out-of-season outbreak of influenza A virus (A/Darwin/6/2021(H3N2)), first detected in Rio de Janeiro in November 2021, and widely spread in the country in the first weeks of 2022. In most Brazilian states, the flu season usually occurs from May to July, starting in the Northeast region and spreading to the South.[1] The simultaneous transmission of COVID-19 and influenza in 2022 resulted in a significant increase in demand for hospital beds, but the country's case-fatality rates associated with the most severe forms of these diseases during this period are unknown.

In this nationwide ecological study, we estimated the case-fatality rates and risk of death from COVID-19 and influenza A/H3N2. Brazil has a geographic area of ~8.5 million square kilometers and a population of *circa* 213 million people. In addition, the country comprises 26 states and one federal administrative district and is divided into five regions: North (seven states), Northeast (nine states), Midwest (three states and one federal district), Southeast (four states), and South (three states). The human development

Table 1
Case-fatality rates and risk of death among hospitalized patients with COVID-19 compared to hospitalized patients with influenza A/H3N2 infection in Brazil.

Variables	COVID-19			Influenza A/H3N2			RR (95% CI)	*p*-Value
	Cases	Deaths	CFR (%)	Cases	Deaths	CFR (%)		
Brazil	99,049	29,727	30.0	4779	852	17.8	1.7 (1.6–1.8)	<0.001
*Region**								
North	5398	1585	29.4	134	34	25.4	1.2 (0.8–1.6)	0.329
Northeast	15,833	5401	34.1	1242	313	25.2	1.4 (1.2–1.5)	<0.001
Midwest	8284	2301	27.8	601	103	17.1	1.6 (1.4–1.9)	<0.001
Southeast	50,369	15,398	30.6	1942	302	15.6	2.0 (1.8–2.2)	<0.001
South	19,138	5027	26.3	860	100	11.6	2.6 (1.9–2.7)	<0.001
*Sex***								
Male	50,888	15,981	31.4	2172	393	18.1	1.7 (1.6–1.9)	<0.001
Female	48,150	13,743	28.5	2607	459	17.6	1.6 (1.5–1.8)	<0.001
Age (years)								
<1	2324	115	4.9	213	5	2.3	2.1 (0.9–5.1)	0.098
1–5	2334	83	3.6	396	11	2.8	1.3 (0.7–2.4)	0.435
6–19	2387	161	6.7	339	12	3.5	1.9 (1.1–3.4)	0.028
20–39	9080	931	10.3	495	45	9.1	1.1 (0.9–1.5)	0.408
40–59	17,228	3709	21.5	606	119	19.6	1.1 (0.9–1.3)	0.270
60–69	16,114	4828	30.0	677	132	19.5	1.5 (1.3–1.8)	<0.001
70–79	20,783	7238	34.8	942	203	21.5	1.6 (1.4–1.8)	<0.001
≥80	28,799	12,662	44.0	1111	325	29.3	1.5 (1.4–1.7)	<0.001
*Race/ethnicity****								
White	46,829	14,303	30.5	1979	323	16.3	1.9 (1.7–2.1)	<0.001
Black	3848	1372	35.7	177	49	27.7	1.3 (1.0–1.6)	0.040
East Asian	911	301	33.0	40	8	20.0	1.7 (0.9 - 3.1)	0.116
Brown	31,114	9724	31.3	1738	344	19.8	1.6 (1.4 - 1.7)	< 0.001
Indigenous	192	42	21.9	53	9	17.0	1.3 (0.7–2.5)	0.447

Asterisks refer to missing data for cases / deaths associated with COVID-19 or influenza according to each variable: *region, **sex, and ***race/ethinicity.
Region*: COVID-19: 27 cases and 15 deaths.
Sex**: COVID-19: 11 cases and 3 deaths.
Race/ethnicity***: COVID-19: 16,155 cases and 3985 deaths; Influenza: 792 cases and 119 deaths.
CFR, case-fatality rate; RR, relative risk; CI, confidence interval.

index (HDI) is 0.765 and the poorest regions of the country are the North (HDI 0.730) and Northeast (HDI 0.715) regions.

We included all hospitalized patients with laboratory-confirmed SARS-CoV-2 or influenza A/H3N2 infection from January 2 to March 12, 2022. The number of cases and deaths by COVID-19 and influenza was obtained from the SIVEP-Gripe dataset (https://opendatasus.saude.gov.br/dataset/srag-2021-e-2022), which is a deidentified public domain database established by the Brazilian Ministry of Health for the surveillance of severe acute respiratory syndrome. Data on sex, age, race, and distribution by geographic region were described. Case-fatality rates were calculated based on the number of deaths divided by the total number of confirmed cases for each disease. Differences in case-fatality rates between diseases as age increased were analyzed by using the Cochran-Armitage test for trend. We also estimated the relative risk (RR) of death by comparing hospitalized patients with COVID-19 to those with influenza according to the variables of interest. The significance level was set as 0.05. Data were analyzed by using JASP software version 0.13 (JASP Team, Amsterdam, Netherlands).

During the first 10 epidemiological weeks of 2022, 99,049 patients with COVID-19 and 4779 patients with influenza were hospitalized in Brazil. A total of 29,727 deaths associated with COVID-19 and 852 deaths from influenza were registered and the case-fatality rates were 30% and 17.8%, respectively. The highest lethality rates for both diseases were observed among men, Blacks, and people over 80 years of age. The Northeast and Southeast regions had the highest case-fatality rates for COVID-19, while the North and Northeast had the highest lethality for influenza (Table 1; Fig. 1 – Supplementary file). Furthermore, we found that differences in case-fatality rates between COVID-19 and influenza tend to increase with increasing age ($p < 0.001$) (Fig. 2 – Supplementary file). The results of this study showed that hospitalized patients with COVID-19 had approximately two-fold increased risk of death compared to those hospitalized with influenza infection (RR = 1.7; 95% CI 1.6–1.8; $p < 0.001$). The risk of death from COVID-19 was higher than from influenza in all geographic regions of the country (except for the North region); in both sexes; white, black, or mixed race; and among those aged 6 to 19 years and over 60 years old (Table 1).

The overall results of this population-based study showed that case-fatality rates for COVID-19 and influenza were higher in the poorest regions of the country, among Blacks, and older individuals. Brazil has large social and economic disparities, which may explain the higher occurrence of deaths from these diseases in individuals living in more deprived areas. In addition, there is evidence that mortality from viral respiratory diseases is higher among older adults[2,3] and is associated with the presence of inherent frailties and multiple morbidities, immunosenescence, and a lower immune response to vaccines.[4] Our findings also strengthen the evidence that individuals with COVID-19 have an increased risk of death compared to those with influenza infection.[5] It has been suggested that disease severity, prolonged hospital stay, and insufficient therapeutic options are possible contributing factors to the increased risk for mortality among hospitalized patients with COVID-19.[6] Furthermore, there is emerging evidence that SARS-CoV-2 infection can lead to a higher inflammatory state associated with dysregulation of the type-I interferon (IFN) response and its downstream cytokine signatures than other respiratory viruses, including influenza.[7]

Although the influenza H3N2 (Darwin) first circulated in Brazil from the end of 2021, it is possible that a cross reactivity antibody response from past exposure to other types of influenza virus provided a certain grade of protection against the disease.[8]

A "cross-protection" against the Darwin strain may also have been achieved through the flu vaccine available in 2021 in the country, which may have influenced lethality rates for the out-of-season influenza. It is important to highlight that vaccine coverage for the Brazilian population against COVID-19 at the beginning of 2022 was approximately 67%, and although the Omicron variant was associated with less severe outcomes than Delta and the original SARS-CoV-2 strain[9], it has been shown that this emerging variant of concern is characterized by evading vaccine-induced immunity and high levels of transmission.[10] Therefore, the third wave driven by Omicron in Brazil may have led to significant morbidity especially in older people, unvaccinated or partially vaccinated individuals and vulnerable populations, with a high case-fatality rate among those with the most severe forms of COVID-19 requiring hospitalization.[11]

The results of this study showed that the case-fatality rates and risk of death from COVID-19 and influenza A/H3N2 in Brazil were influenced by socioeconomic factors and age. Furthermore, we found evidence from population-based data that the risk of death from COVID-19 is higher than that from influenza virus infection.

Authors' contributions

All authors contributed equally to the manuscript.

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Conflict of interest

The authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.eimc.2022.05.015.

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