ORIGINAL ARTICLE

Change in the epidemiological profile of severe acute respiratory syndrome in the Brazilian pediatric population: indication of COVID-19 subnotification

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Abstract

Introduction: The impact of COVID-19 on the Brazilian pediatric population may be underestimated by underreporting. This study compares the incidence of hospitalizations and deaths due to severe acute respiratory syndrome (SARS) and etiologies in children between 2019 and 2020. **Methods:** Epidemiological study carried out by consulting InfoGripe. Data referring to epidemiological weeks 1 to 25 of the years 2019 and 2020 were consulted, analyzed using the SPSS 26.0 program. **Results:** Comparing the years 2019 and 2020, we observed reduction in the incidence rate (per 100,000) of hospitalizations for SARS in the 0-4 year age group from 4.023 to 2.980 ($p = 0.05$), and an increase in the other age groups, in schoolchildren, 0.353 to 0.618 ($p = 0.009$) and among adolescents, 0.115 to 0.393 ($p = 0.002$). There was an increase in deaths from 0.013 to 0.017 ($p = 0.05$) between 5-9 years, and from 0.009 to 0.029 ($p = 0.001$) between 10-19 years. In relation to "unknown etiology", the incidence of hospitalizations increased from 0.294 to 1.454 ($p = 0.007$) and deaths from 0.03 to 0.28 ($p = 0.004$). **Conclusion:** The incidence of hospitalizations and deaths due to SARS in 2020 in children aged 5-9 and 10-19 years was higher than in 2019. The 3.4-fold increase in the number of cases, and 9.3-fold increase in deaths from SARS without a defined etiology in 2020 may suggests an important underreporting by COVID-19 in Brazil. Further studies are needed to assess the extent and impact of SARS-CoV-2 in children.

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INTRODUCTION

The new coronavirus (SARS-CoV-2) is an RNA virus of lineage B, subgenus Sarbecovirus, sub-family Coronaviridae, which causes the disease called COVID-19, transmitted from person to person by droplets, direct contact with infected secretions, generated aerosols by therapeutic procedures or fomites[1]. The initial outbreak was reported in the city of Wuhan, Hubei province, China, on December 31, 2019, and on March 11, 2020, the World Health Organization declared it a pandemic[2,3].

SARS-CoV-2 infection causes more exuberant conditions in adults and the elderly, while the pediatric population has a mild or even asymptomatic clinical course, with better prognosis and rare reports of death. In the largest series of pediatric cases, about 90% of the 2,143 children evaluated with positive tests had infection without symptoms or mild to moderate symptoms[4].

The reasons for the less aggressive virus in the child population are still being investigated. The infection activates cellular and humoral, innate and adaptive immunity, and can trigger an exacerbated inflammatory response of the host, with severe acute respiratory syndrome (SARS), sepsis and multiple organ dysfunction syndrome. Factors such as the immaturity of the children's adaptive immune system, BCG vaccination and previous infections by the respiratory syncytial virus, seem to be related to less viral invasion and less exuberant inflammatory response[5,6]. On the other hand, with the evolution of the pandemic and significant increase in the number of infected children in Brazil and in the world, acute and severe cases have been reported in children and adolescents, possibly associated with COVID-19. The cases have been described as SARS and Multisystemic Inflammatory Syndrome, potentially fatal[7]. Traditionally, the main etiologies that result in SARS are viruses (Influenza A, dengue, Respiratory Syncytial Virus, Adenovirus, Hantavirus and Coronavirus), and bacteria (Pneumococcus, Legionella sp., Leptospirosis, etc.)[8]. However, with the emergence of the SARS-CoV-2 pandemic, a new virus subtype has become an important etiology of SARS, causing everything from asymptomatic to exuberant manifestations in the elderly, adults and even adolescents and infected children[4,7].

On June 27, 2020, four months after the confirmation of the first COVID-19 case in Brazil, Brazil had 1,313,667 confirmed cases and 57,070 deaths, being the second country with the highest number of confirmed deaths by the disease. However, despite the significant and well-known health, economic, political and social impacts caused by the SARS-CoV-2, the repercussions can be even more severe due to the large volume of underreporting and the small number of tests performed[9].

It is an estimate that the number of confirmed and notified cases of COVID-19 corresponds to only 32% (95% CI 25-38%) of the total symptomatic cases in Brazil[10]. Until May 29, 2020, there were only 2.28 tests performed per one thousand inhabitants, an amount substantially lower than the average found in countries such as the USA (48.96/thousand inhabitants), Portugal (81.7/thousand inhabitants) and Spain (54.23/thousand inhabitants)[11]. Another recent study shows that the actual number of cases is about 11 times higher than reported. A scenario requires caution, since the absence of reliable data can lead to erroneous interpretations and mistaken measures of planning and action to control the disease[12].

In view of the significant contingent of underreporting and the emergence of serious, potentially fatal cases among children and adolescents, it is essential to seek tools to assist in the real understanding of the current epidemiological situation and the impact of the disease in these age groups. In this sense, the comparative analysis of the incidence of cases and deaths from SARS in the years 2019 and 2020 is relevant, since a possible increase in confirmed cases without a defined etiological diagnosis may represent underreported cases of COVID-19 in the pediatric population. This study aims to compare the incidence of SARS in the pediatric age group in the epidemiological weeks 1 to 25 in 2019 and 2020, in order to find an unexpected increase in the number of cases without a defined etiological diagnosis that, in reality, may represent undiagnosed cases of SARS-CoV-2.

METHODS

This is a descriptive epidemiological study, which data were obtained by consulting the InfoGripe database, which monitors reported cases of Severe Acute Respiratory Syndrome (SARS) at SINAN (Information System for Notifiable Diseases), made available at the electronic address http://info.gripe.fiocruz.br/, accessed on 06/27/2020.

The study population consists of all cases of hospitalizations and deaths from SARS, defined as "SARS" and "deaths by SARS" respectively, in three age groups: 0 to 4 years, 5 to 9 years, 10 to 19 years, reported between epidemiological weeks 1 to 25 of the years 2019 and 2020. Data on the incidence of hospitalizations and deaths due to SARS according to etiology represent the total population of cases without specification of age groups, and are categorized as "Unknown etiology", "No SARS CoV-2", "SARS CoV-2", reported in the same period. (I think it is necessary to leave it out, as it does not divide into age groups here. All issues are presented as provided by the InfoGripe platform, with the denominator consisting of 100,000 inhabitants without distinction as to age, thus representing the entire Brazilian population.

We ran statistical analyzes using the SPSS (Statistical Package for Social Science) version 26.0. We checked the data parameters using the Shapiro-Wilk test. For incidence distribution, we used the scatterplots and the Boxplot. We compared the 2019 and 2020 averages of the 25-week incidences per 100,000 inhabitants using the Mann-Whitney test. In all analyzes, we adopted a significance level of 5% ($p \leq 0.05$).

RESULTS

Until the epidemiological week 25 of the year 2020, the average incidence (per 100,000) of SARS in the population from 0 to 19 years old was 3,991 (SD ± 2,765) (Table 1). Considering the age group with the highest representativeness of SRAS cases, we found an incidence of 2.980 (SD ± 2.219) in the age group 0-4 years. In contrast, the lowest incidence of SARS occurred between 10-19 years, with a value of 0.393 (SD ± 0.276), and between 5-9 years the incidence was 0.618 (SD ± 0.389). When comparing the incidence of SARS up to that week in the 2019-2020 biennium, there was a reduction in the incidence of SARS between 0-4 years (p value = 0.05) and a statistically significant increase in the incidence of the disease between the 5- 9 (p = 0.009) and 10-19 years (p = 0.002). Thus, the incidence of SARS in 2020 between 10-19 years was about 3.5 times higher than in 2019, while between 5-9 years it was approximately 1.75 times higher.
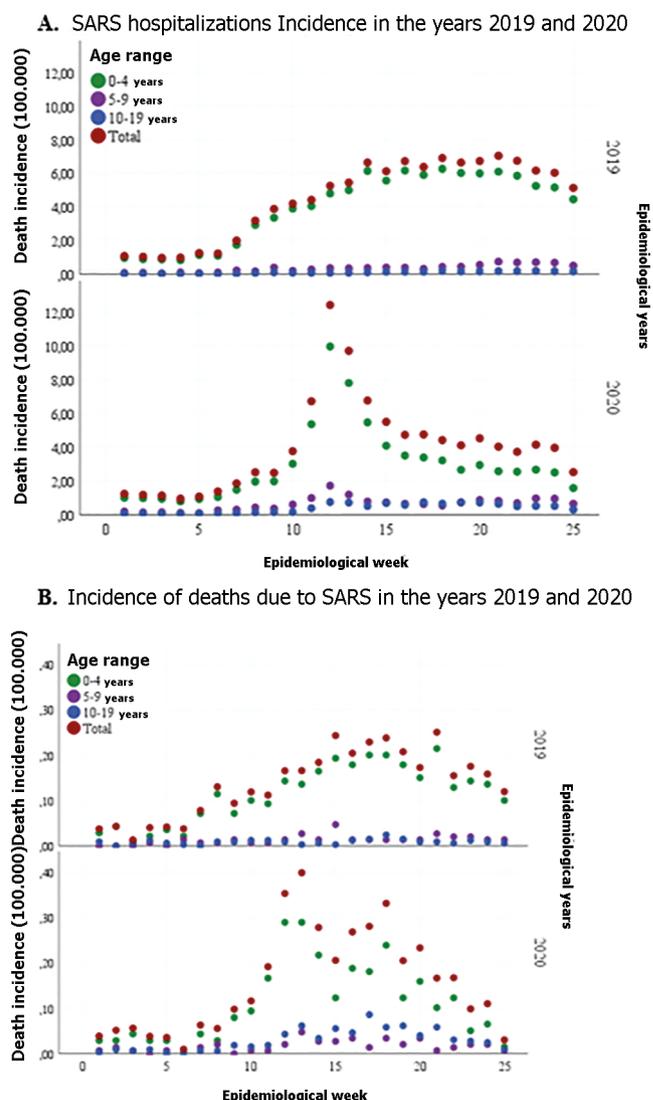
In the analysis of the incidence of deaths due to SARS, this association was maintained (Table 1). There was an increase, with statistical significance, in the incidence of deaths due to SARS in the 5-9 age groups, from 0.013 to 0.017 (p = 0.05) and between 10-19 years from 0.009 to 0.029 (p = 0.001). Thus, the death record in 2020 was 1.3 times higher in the age group of 5-9 years and 3.2 times higher among adolescents (10-19 years).

Analyzing the distribution of the incidence of hospitalizations for SARS in the 2019-2020 biennium, in 2020 there was an increase in the total incidence of hospitalizations from the 10th epidemiological week. This increase in incidence occurred in all age groups analyzed, but it was substantially significant in the age group 0-4 years, reaching a peak incidence in the 12th week, with a value of approximately 10 to 100,000. In the 5-9 and 10-19 age groups, the incidence was also higher than that found in 2019, but the peak at the 12th week was less expressive, with around 1.72 and 0.74 for every 100,000, respectively (Graph 1 A).

Table 1. Incidence of hospitalizations and deaths due to SARS in the epidemiological weeks 1 to 25 in the years 2019 and 2020, by age group.

	Incidence /100.000 (Mean ± Standard deviation)		p*
	2019	**2020**	
SARS			
0-4 years	4.023 ± 2.067	2.980 ± 2.219	0.05
5-9 years	0.353 ± 0.217	0.618 ± 0.389	0.009
10-19 years	0.115 ± 0.062	0.393 ± 0.276	0.002
Total	4.491 ± 2.303	3.991 ± 2.765	0.24
Death			
0-4 years	0.115 ± 0.064	0.109 ± 0.086	0.63
5-9 years	0.013 ± 0.010	0.017 ± 0.012	0.05
10-19 years	0.009 ± 0.005	0.029 ± 0.024	0.001
Total	0.136 ± 0.073	0.155 ± 0.114	0.76

*Teste de Mann-Whitney.

A. SARS hospitalizations Incidence in the years 2019 and 2020

B. Incidence of deaths due to SARS in the years 2019 and 2020

Graph 1. Incidence of hospitalizations and deaths due to SARS during epidemiological weeks 1 to 25 by age group in the periods of 2019 and 2020.

Regarding the dispersion of the incidence of deaths due to SARS in the same period, from the 9th week on, in most weeks, the incidence in 2020 was higher than the incidence in 2019. The peak incidence in 2020, 0.377 deaths in 100,000, occurred in the 13th epidemiological week, and it was higher than the value found in the previous year. The age group of 0-4 years had a higher incidence of deaths in the 13th week, with around 0.29. Finally, the highest incidence of deaths between 5-9 occurred in the 14th week, around 0.027, and between 10-19 years, the peak incidence of deaths from SARS was in the 17th week, with an approximate value of 0.086 (Graph 1 B).

As for the incidence of hospitalizations for SARS according to etiology (Table 2) in 2020 until the epidemiological week # 25, it was as follows: the etiology defined as "SARS-CoV2" was 1.712 (SD ± 1.849), while by etiology defined as "

Tabela 2. Incidence of hospitalizations and deaths due to SARS, according to "SARS-CoV-2", "Non-SARS CoV-2" and "Unknown etiology" etiology, without distinction as to the age range in epidemiological weeks 1 to 25 in 2019 and 2020.
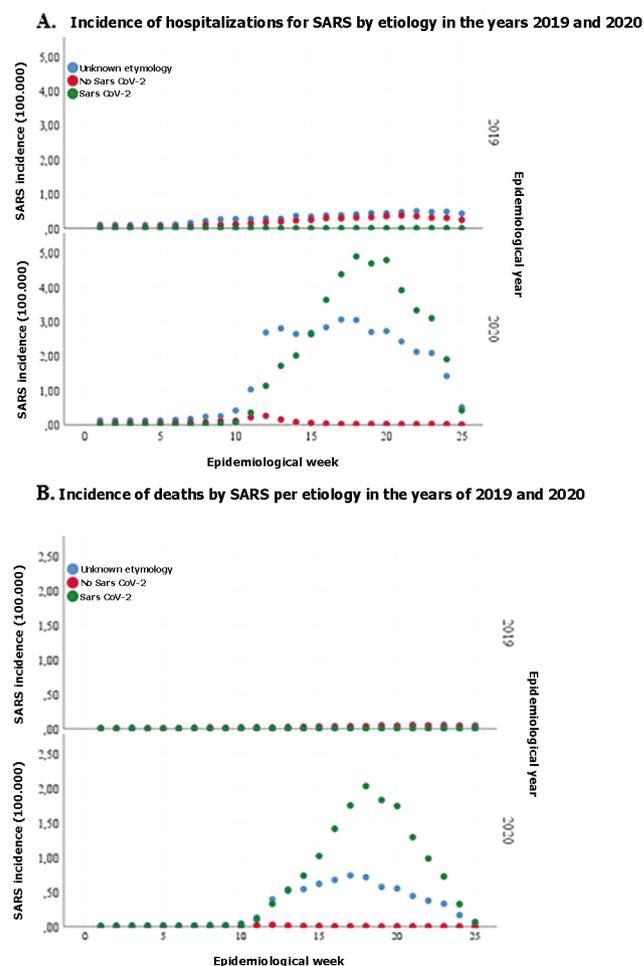
	Incidência (100.000)		p*
	2019	2020	
SARS			
Unknown etiology	0.294 ± 0.143	1.454 ± 1.214	0.007
No SARS CoV-2	0.183 ± 0.123	0.054 ± 0.063	<0.001
SARS-CoV-2	Na	1.712 ± 1.849	Na
Death			
Unknown etiology	0.030 ± 0.016	0.280 ± 0.270	0.004
No SARS CoV-2	0.017 ± 0.013	0.005 ± 0.006	<0.001
SARS-CoV-2	Na	0.594 ± 0.703	Na

*Mann-Whitney test; NA = not applicable.

No SARS Cov-2 "was 0.054 (SD ± 0.063), and for" Unknown etiology "it was 1.454 (SD ± 1.214) per 100,000 inhabitants. Comparing the 2019-2020 biennium, there was a statistically significant increase (p = 0.007) in the incidence of cases by "Unknown etiology" in the year 2020, 4.9 times. Regarding the "No SARS-CoV-2" etiology, the incidence in 2020 was 3.4 times lower (*p* <0.001) than in 2019. The comparison of deaths by etiology in the two periods followed a similar pattern. In 2020, the incidence of deaths due to "Unknown etiology" was 9.3 times higher (*p* = 0.004) than that of the same period in the previous year. On the other hand, the incidence of deaths by "No SARS CoV-2" etiology decreased 3.4 times in 2020 compared to 2019.

Graph 2 shows that, in relation to hospitalizations (Graph 2A) and deaths dispersion (Graph 2B) by SARS according to etiology, weeks 1 to 25 of the year 2019 and the first 9 weeks of 2020 had an epidemic distribution, without outliner points. As of week 9 of the year 2020, the incidences for "Unknown etiology" showed a substantial increase, being higher than the incidences of all corresponding weeks in the year 2019.

Regarding the defined etiology "Non SARS CoV-2", the main viruses were Influenza A and RSV (Respiratory Syncytial Virus). The incidence of hospitalizations for SARS due to Influenza A in 2019 was 0.065 (SD ± 0.063) for 100,000 and in 2020 it was 0.021 (SD ± 0.029), with a 68% reduction (*p* = 0.02) in relation to the same period in the previous year. Similarly, the incidence of hospitalizations for SARS due to RSV also decreased from 0.099 (SD ± 0.062) in 2019 to 0.017 (SD ± 0.020) in 2020, expressing a reduction of 83% (*p* < 0.001). As for deaths, the incidence of SARS due to Influenza A in 2019 was 0.011 (SD ± 0.011) and in 2020 it was 0.002 (SD ± 0.004), a reduction of 82% (*p* value = 0.001). The incidence of deaths by SARS caused by RSV was 0.004 (SD ± 0.003) in 2019 and 0.001 (SD ± 0.001), a 75% reduction (*p* value < 0.001).

A. Incidence of hospitalizations for SARS by etiology in the years 2019 and 2020

B. Incidence of deaths by SARS per etiology in the years of 2019 and 2020

Graph 2. shows that, in relation to hospitalizations (Graph 2A) and deaths dispersion (Graph 2B) by SARS according to etiology, weeks 1 to 25 of the year 2019 and the first 9 weeks of 2020 had an epidemic distribution, without outliner points. As of week 9 of the year 2020, the incidences for "Unknown etiology" showed a substantial increase, being higher than the incidences of all corresponding weeks in the year 2019.

DISCUSSION

When comparing the first 25 epidemiological weeks of 2019 and 2020, the present study found an increased incidence of hospitalizations and deaths from SARS in the 5-9 and 10-19 age groups; with regards to the etiology from all age groups, there was a reduction in hospitalizations and deaths due to SARS etiology, defined as "Not SARS-CoV-2" and a significant increase in cases of "unknown etiology".

The important changes in the epidemiological profile of SARS reflect the presence of the new etiological agent that causes COVID-19 and the behavioral changes brought about by the quarantine implementation. Social distancing, even if done in a partial way, reduces the circulation of all viruses and bacteria, which justifies the reduction of cases and deaths of

etiology defined as "Non-SARS-CoV2", and this is reflected mainly in the age group from 0 to 4 years, population more susceptible to SARS by etiologic agents such as RSV and Influenza.

The significant increase in hospitalizations and deaths due to SARS of "Unknown etiology" amid the pandemic of COVID-19, suggests that the unexpected increase in cases without etiological diagnosis, in fact, may represent cases of undiagnosed SARS-CoV-2, either due to the low availability of tests or due to their low sensitivity. This hypothesis corroborates the fact that, in the first days after infection, serological tests show sensitivity between 18.4% and 46.7%. In viral RNA detection tests, using RT-PCR, the sensitivity identified was 44.2%[13,14]. Thus, it is feasible to state that there is a huge contingent of false-negative results, especially in early phases of the infections.

In this study, due to the low effectiveness in confirming cases infected with COVID-19 in Brazil, we assume that there is a big difference between the number of suspected cases and those of reported cases[12]. Through the results found, we see that this also applies to the pediatric population, as per reported in the present study, the incidence of hospitalizations for unknown Etiology in 2020 was 4.9 times higher than in 2019. Among the numerous justifications for this disproportion and the probable underreporting of hospitalizations due to SARS-CoV-2, the following stand out: operational difficulties for carrying out tests; low availability of new exams; restricted ability to analyze results; low sensitivity of diagnostic tests, and logistics difficulties in the distribution of tests in a country of continental dimensions such as Brazil[12,15].

The methodology of the present study was based on the analysis of secondary databases and, due to the source of information available, some limitations are imposed.

First, in 2019, there was a lower number of hospitalizations or deaths reported due to SARS; whereas in 2020, in more than half of the cases the notification occurred. Certainly, hospitalizations and deaths due to SARS in 2019 were predominantly of unknown etiology because there is no such motivation to elucidate it when compared to the 2020 pandemic scenario. The two years are therefore not comparable in terms of etiology. Thus, it is not possible to state categorically that the unknown etiology in 2020 means a large number of SARS-CoV-2 underreported. However, it is feasible to infer that in this contingent of cases, there may be cases of unnotified COVID-19, representing an indication of underreporting.

On the other hand, the etiologies of hospitalizations and deaths due to SARS represent the total population, regardless of age, so it is not possible to state with precision that the data provided apply to the pediatric population. The stratification of these data, by age, would be essential for a more assertive understanding of the epidemiological situation. Even so, there was a statistically significant reduction in the incidence of hospitalizations and deaths from Influenza A and RSV, important etiological agents responsible for SARS between 0-4 years[8]. Therefore, it is possible that the reduction

in hospitalizations and deaths by these agents also extends to the pediatric population and a plausible explanation for this decrease is the social distance adopted during the pandemic, which significantly reduced the contact with secretions and droplets contaminated by these viruses.

Another relevant aspect that compromises the full understanding of the current epidemiological situation is the diagnosis or detection bias, due to the emergence of the new coronavirus in Brazil. Because of this worldwide attention to COVID-19, the beginning of hospital protocols and the detection of the first cases in the country, there is a higher likelihood of SARS diagnosis and notification. Thus, the peak of cases close to week 12 may reflect, again, a diagnostic motivation bias, which would have value in increasing the number of SARS diagnoses to the detriment of others, such as pneumonia, flu syndrome, respiratory failure, sepsis, possibly most accomplished in previous years.

Finally, the increase in hospitalizations and deaths due to SARS among schoolchildren and adolescents, added to the increase in cases of "Unknown etiology" may indicate that the underreporting of cases and deaths by COVID-19 in Brazil is also expressive among pediatric patients, and interferes in the understanding of the epidemiological moment experienced by the country, as well as its real seriousness.

Although limited, the available data show an increase in the incidence of hospitalizations and deaths due to SARS in 2019 to 2020 in those over 4 years of age. Thus, it is essential to increase the testing and notification of confirmed cases, as well as to present the etiology data in categories by age. In addition, new studies are essential to assess the extent and impact of SARS-CoV-2 in the pediatric population, providing reliable estimates, and thus guaranteeing the adoption of assertive conducts capable of positively impacting disease control.

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