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Research Article

The Epidemiology of Viruses Causing Acute and Severe Respiratory Diseases in Children, Before and During the COVID-19 Pandemic

Ito CRM[1]*, Sousa JAS[1], Gonçalves LC[2], Silva PAN[2], Santos MO[2], Moreira ALE[2], Pereira AS[2], Peixoto FAO[2], Fonseca JG[2], Wastowski IJ[3], Carneiro LC[1], Avelino MAG[2]

[1]LBMIC, Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiânia, Brazil

[2]Medicine Faculty, Federal University of Goiás, Goiânia, Brazil

[3]Academic Institute of Health and Biological Sciences, State University of Goiás, Goiânia, Brazil

***Corresponding author:** Ito CRM, LBMIC, Institute of Tropical Pathology and Public Health, Federal University of Goiás, Goiânia, Brazil

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Abstract

Viruses are the main pathogens that cause SARI, and children are much affected around the world. Therefore, the aim of this study is to assess the frequency of SARI and SARS cases caused by seasonal viruses in children before and during the COVID-19 pandemic.

Methods: Data were taken from the electronic health surveillance system, and covered children (0 to 14 years of age) hospitalized for SARI and SARS, in the period between January 2013 to August 2021.

Results: Between 2013 and 2019, the number of SARI cases had an average of 18,124 cases per year. In 2020 and 2021, the incidence of hospitalization for acute respiratory infection SARS-CoV-2 only appears in 2020 (61.0%), and RSV 8.6%, but SARS-CoV-2 and RSV increases (37%). SARI is more lethal in children under 1 year of age (44.22%). From 2013 to 2019, the average number of deaths was 3.58%, and the influenza A virus (30.26%) was the most lethal, considering all ages, followed by RSV (23.4%). In children under 01 years of age, RSV (16.12%) and influenza A (9.44%) are the most lethal. In 2020 and 2021, the average of deaths was similar (3%, 2020), 1.8% 2021), and SARS-CoV-2 was the most lethal in all age groups (81.27%) followed by RSV (8.55%) and Human Rhinovirus which was 3.51%.

Conclusion: Influenza is responsible for most deaths from SARI, being the most prevalent RSV in children aged 0 to 01 years, and in the pandemic, SARS-CoV-2 predominated. During the pandemic, the pattern of SARI cases changed both in seasonality and in virus prevalence, due to Brazil's mitigation strategy to contain COVID-19.

Keywords: Coronavirus; Children; Seasonality; Mortality; Mitigation; Epidemiology

Introduction

Acute Respiratory Infections (ARI) are a major public health problem and cause four and a half million deaths among children each year, and children in developing countries are the most affected. In acute respiratory diseases, virus infections are identified in 30%-40% of cases in inpatients and outpatients, when both cell culture and diagnostic techniques are quickly performed [1].

Severe Acute Respiratory Infections (SARI) affect individuals at an early stage (within seven days), with fever symptoms (≥38°C), cough, shortness of breath or difficulty breathing and require hospitalization. Children are very affected by SARI around the world, generating about 1.9 million deaths per year, 70% of these deaths occur in developing countries, and 30% of child deaths are due to this infection [2-6].

The main viral pathogens that cause SARI are the seasonal influenza A and B virus, the influenza A (H1N1) pdm09 strain, Human Metapneumovirus (HMPV), Human Rhinovirus (HRV), Human Adenovirus (HAdV), Human Parainfluenza Virus (HPIV), Respiratory Syncytial Virus (RSV), Human Bocavirus (HBoV), Human Coronavirus (HCoVs) and Enterovirus (EV) [7-9].

In children, infection rates vary at different ages and seasons. In the preschool period, the ADV positivity rate is higher and that of RSV is higher in infants; that of influenza increases with age. The total positive rate of viral infection in different seasons of the year is higher in winter, as is the influenza positivity rate [10].

The world has witnessed three major pandemics in the last century, the first in 1918 with Influenza type A/H1N1, responsible for approximately 50 million deaths, mainly young people. In 1957 the second pandemic occurred, again caused by the Influenza A virus, but with the H2N2 variant and the third-largest pandemic was in 1968, also caused by the Influenza type A, this time with the H3N2 variant, which had around 2 million deaths worldwide [11].

In late 2019, a new outbreak of pneumonia re-emerged in China, which was later named SARS-CoV-2. Severe Acute Respiratory Syndrome (SARS) was classified as a viral respiratory disease caused by a coronavirus associated with SARS, first identified in February 2003 during an outbreak in China and spread to 4 other countries [12].

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SARS is highly transmissible and occurs through symptomatic patients through direct or indirect contact with droplets of respiratory secretions, and can be spread through the air, with an incubation period ranging from 02 to 10 days, which allows the virus to spread over long distances by traveling infected people [13].

Influenza epidemics and pandemics are due to changes in the context of society over the decades and this contributes to the dispersion of new strains, within a solid ecological, social, and spatial scenario [14]. To contain the spread of respiratory viruses and minimize their "wounds", countries adopt personal protection measures (staying at home, wearing masks, and washing hands frequently), and, when there is a pandemic, community measures which reduce mass exposure (closures of establishments, daycare centers, schools, concerts, etc) [15].

More studies are needed to find out whether these strategies of personal and community protection measures to contain the spread of respiratory viruses reduce cases of SARI during the months of the seasonality of viruses, such as RSV and influenza, which are the viruses that most generate cases of respiratory infection in winter and early spring every year. Therefore, the aim of this study is to assess the frequency of acute respiratory infections such as SARI and SARS cases caused by seasonal viruses in children before and during the COVID-19 pandemic.

Materials and Methods

The study was restricted to children and adolescents (0-14 years of age) hospitalized with acute and severe viral respiratory diseases from January 2013 to August 2021. The entire population with data registered and available at Influenza Epidemiological Surveillance Information System (SIVEP), an electronic health surveillance system with mandatory notification for cases of hospitalization due to SARI, [16-19] was used for analysis. According to the Ministry of Health of Brazil, cases should be considered SARS if they meet the following criteria: 1 – fever, even if self-reported; 2 – cough or sore throat; 3 – dyspnea or O2 saturation <95% or respiratory distress.

Data referring to viruses isolated from the cases during the analyzed period were collected, only laboratory identification by polymerase chain reaction or other molecular techniques were considered. Forecast analysis was performed using an Autoregressive Integrated Moving Average model (ARIMA) to perform forecasts for the year 2020 until August 2021, in order to compare the model's forecast with real cases in the same period. For this, the data were transformed using BoxCox. For non-seasonal differentiation, KPSS was used by default; there was no need to perform seasonal differentiation in the data. The model with the best fit, in order to provide the smallest mean squared prediction error, was, by default, ARIMA (1.1,1). The four error measures used were Root Mean Square Error (RMSE), Mean Absolute Error (MAE), Mean Percentage Error (MPE), and Mean Absolute Percentage Error (MAPE). Residual analysis showed that the residuals were close to the errors and, therefore, presented an average close to zero, constant variance, and was not auto correlated, which denotes white noise. ARIMA was built using the approach proposed by Box-Jenkins.

Results

When considering the period from 2013 to 2019, the number of SARI cases had an average of 18,124 cases per year, with little variation among the years. The years 2013, 2014, and 2015 showed the lowest number of cases, emphasizing 2015 the year with the lowest number (8293), and 2019 the year with the highest number (27036). The subsequent years showed a considerable increase in cases; it appears that the number of cases in 2016, 2018, and 2019 was above the average for the period studied. In 2016 there was an epidemiological outbreak of influenza.

The years 2020 and 2021 present many cases of children and adolescents hospitalized for respiratory infection, with an incidence much higher than the years 2013 to 2019. There were (68,100) cases observed in 2020 and (62772) cases until August 31, 2021. The sudden increase in acute respiratory infection cases is due to the new corona virus pandemic, which causes severe acute respiratory syndrome caused by the SARS-CoV-2 virus. It is observed that the adjusted curve, considering the total number of annual cases, shows an increase due to many cases in 2020 and 2021 (Figure 1).

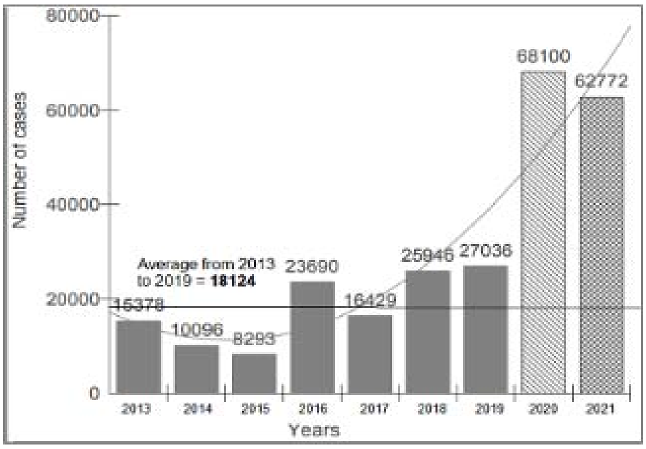

Figure 1: Total SARI/SARS cases accumulated per year between 2013 and 2021, Brazil.

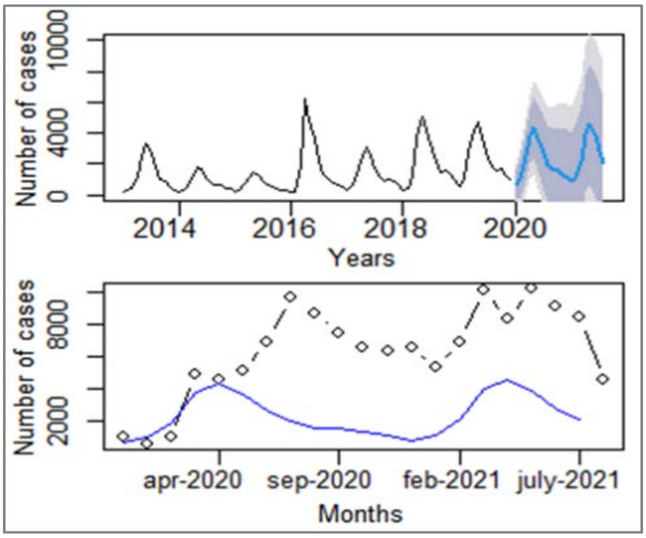

Figure 2: Time series of SARI/SARS cases in Brazil and ARIMA forecast for 2020 and 2021.

Table 1: Comparison among months and years of total SRAG cases, Brazil.

Kruskal-Wallis (Student-Newman-Keuls)					
Difference between posts					
Comparisons	Dif. Posts	p-value	Comparisons	Dif. Posts	p-value
Jan < Mar	37,8	0,008	June > Nov	39,0	0,008
Jan < Apr	53,1	<0.001	June > Dec	44,3	0,003
Jan < May	61,6	<0.001	July > Nov	31,6	0,031
Jan < June	58,8	<0.001	July > Dec	37,0	0,012
Jan < July	51,4	<0.001	2018 > 2014	25,1	0,04
Jan < Aug	41,3	0,004	2018 > 2015	30,9	0,012
Jan < Sept	29,1	0,048	2019 > 2014	29,8	0,015
Feb < Mar	28,1	0,048	2019 > 2015	35,6	0,004
Feb < Apr	43,4	0,002	2020 > 2013	43,9	<0.001
Feb < May	51,9	<0.001	2020 > 2014	51,5	<0.001
Feb < June	48,1	<0.001	2020 > 2015	57,2	<0.001
Feb < July	41,8	0,003	2020 > 2016	35,4	0,004
Feb < Oct	31,7	0,026	2020 > 2017	37,4	0,002
Apr > Nov	33,3	0,023	2020 > 2018	26,4	0,032
Apr > Dec	38,6	0,008	2021 > 2013	57,7	<0.001
May > Sept	32,5	0,027	2021 > 2014	65,2	<0.001
May > Oct	31,8	0,022	2021 > 2015	71,0	<0.001
May > Nov	41,8	0,004	2021 > 2016	49,2	<0.001
May > Dec	47,1	0,001	2021 > 2017	51,1	<0.001
June > Sept	29,7	0,043	2021 > 2018	40,1	0,003
June > Oct	32,3	0,028	2021 > 2019	35,4	0,01

A time-series analysis to predict SARS cases from January 2020 to August 2021 was performed. When considering cases between 2013 and 2019, it was considered a standard incidence. ARIMA's forecast verified that, in the absence of the new corona virus pandemic, the number of SARI cases in children and adolescents aged 0 to 14 years would follow the pattern of previous years, with approximately twenty thousand cases per year. The p-value calculated for the model was <0.001, showing statistical significance for the ARIMA model. The residuals of the model used were not auto correlated, confirming that the accuracy of the model is good (Figure 2).

The monthly distribution of SARI and SARS cases followed an annual seasonality, showing a routine increase between the months of April and June. However, cases start to increase in March, having a peak in May and decreasing in the following three months (June to August). In (Figure 3), it is possible to observe the distribution of monthly cases accumulated between 2013 and August 2021. The very high points in the graph are outliers, that is, very large values that are substantially far from the average of cases given as the monthly standard. All outliers refer to values from the years 2020 or 2021, for these years there were many cases of SARS, being much higher than the expected monthly average.

Figure 4 shows that the first two months of each year showed few cases, except for the year 2021, which is being influenced by the new corona virus pandemic. The seasonality period is always the same from 2013 to 2019, however, unlike previous years, in 2020, the peak was in July, two months ahead of the frequently observed seasonal peak. In the year 2021, the peak was again in the month of May, like the years before the pandemic. In 2020, the number of cases between January and February is considered standard, following the average of previous years, this is since the pandemic reached large proportions in Brazil only in March. In May 2020, seasonality began, like what happened in the years before the pandemic, but with several cases above the standard. The number of cases remains high in the following months until August 2021.

The KW test was performed to compare the mean of cases among the monthly accumulated and showed a significant difference between the months of January and May, when compared to the other months of the year (MDp) = 61.6; p<0.001. The month of May presented significant MDp when compared to January, February, September, October, November, and December, demonstrating the largest number of cases among the mentioned months. Comparisons among years show that 2020 and 2021 have significant MDp, with a greater number of cases compared to the other years studied. There was no significant difference between 2020 and 2021. The year with

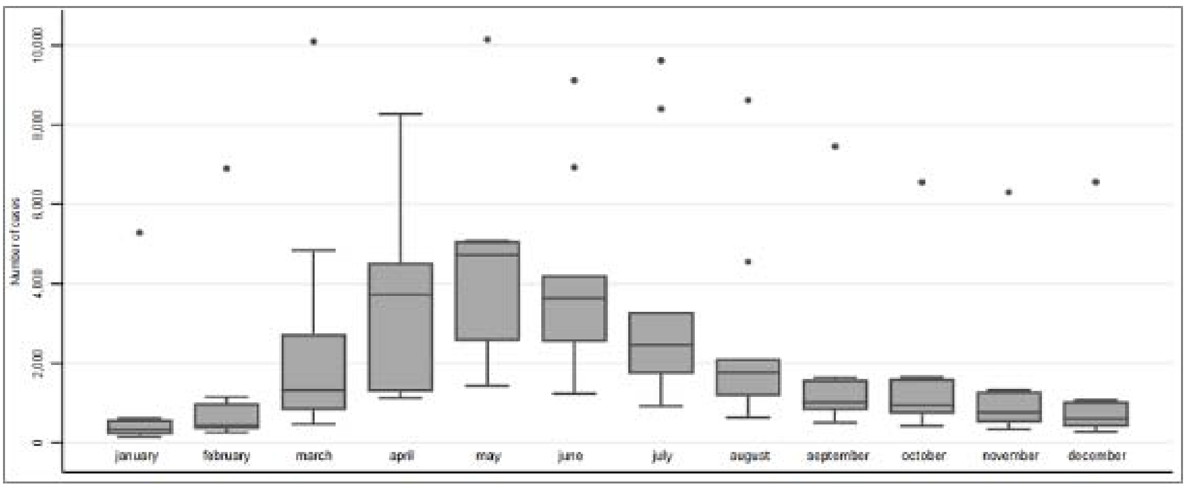

Figure 3: Total SARI/SARS cases accumulated per month between 2013 and 2021, Brazil.

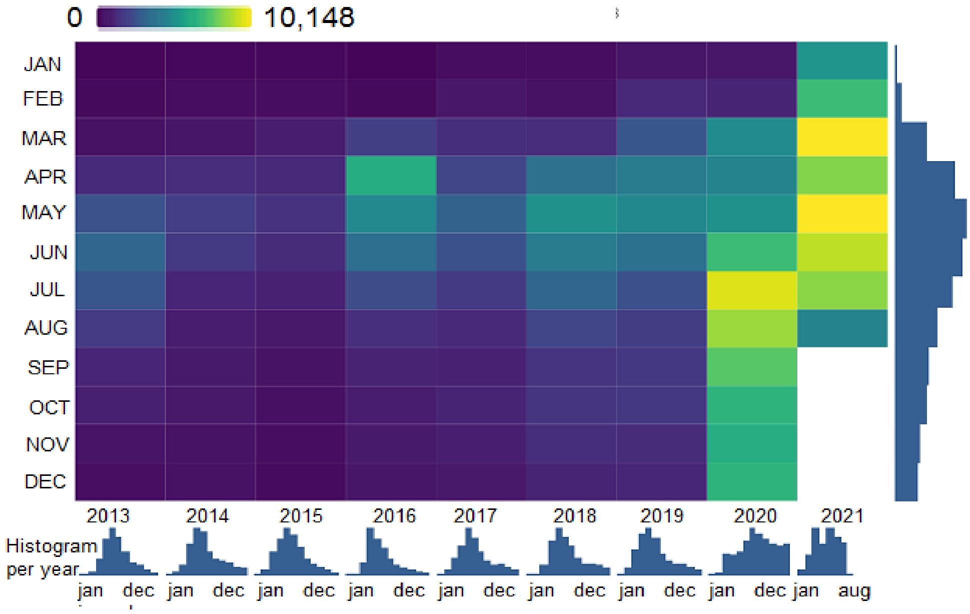

Figure 4: Heat map for SARI/SARS cases in Brazil from 2013 to 2021.

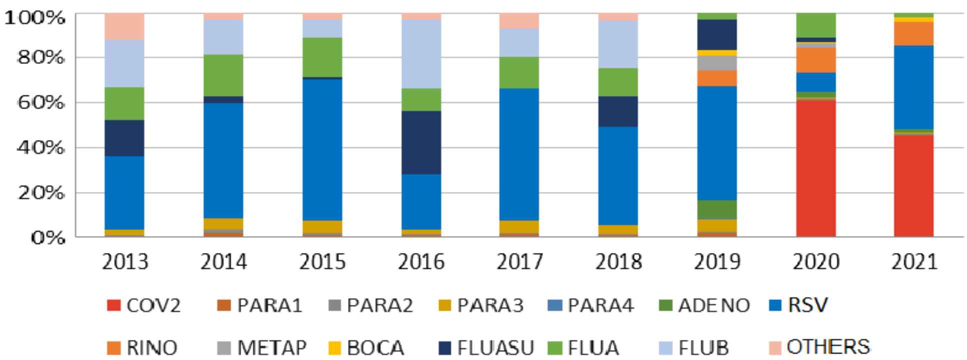

Figure 5: Prevalence of SARI/SARS-causing viruses per year from 2013 to 2021, Brazil.

the greatest difference was 2021 and 2015 (MDp) = 71.0; p<0.001.

Among the different pathogens causing SARI, the RSV is the most prevalent throughout the period from 2013 to 2021. However, there is a considerable decrease in 2016, when the number of people infected with influenza increases (-b and influenza-a subtype). In 2015, only 1.1% of cases that had laboratory identification were influenza-a subtype. Soon after 2016, influenza-a subtype accounted for 28.2% of cases of SARI, being the second most prevalent for this year, behind only influenza-b.

Influenza-a and influenza-b SARI cases show great variation over the period. On the other hand, parainfluenza-1, 2, 3, and 4 remain constant, with a very small rate. Parainfluenza-3 is the one with the highest rate, ranging from 2.2% to 5.8%, when considering the years 2013 to 2019. From 2020 and 2021, there is a drop for all four types of par influenzas. Note that from 2019, 2020 and 2021 Rhinovirus appears in the data (7%, 10.8%, and 10.8%) respectively.

Coronavirus-2 SARS cases only appear in 2020, changing the entire pattern observed in previous years, accounting for 61.0% of identified cases. Respiratory syncytial virus, previously responsible for 50% of cases on average, drops to 8.6%. In 2021, there is a decrease in cases of corona virus 2, and the circulation of RSV increases again, 37% of identified cases. (Figure 5) shows all the data regarding the viruses between 2013 and 2021.

Making a cut in the data, from 2013 to 2019, the average of deaths from SARI was 3.58% (<3.3 - >4.1), and when individually, the influenza A virus (30.26%) was the most lethal, considering all ages, followed by RSV (23.4%). However, the prevalence profile is not the same when analyzed by age group, as follows: influenza A followed by influenza B subtype for children between 1 and 2 (8.78% – 6.63%), 3 and 4 (3.75% – 2.82%), 5 and 6 (2.32% – 1.60%), and 7 to 10 (3.15% – 2.04%), years respectively. For children under 01 years of age, the most prevalent virus was RSV (16.12%) and influenza A (9.44%). Regarding the incidence, it was found that all SARI-causing viruses with evolution to death occurred with a higher proportion in children under 01 years of age (44.22%), an age group where there are more cases of SARI, and the lowest incidence rate was in children between 5 to 6 years (5.53%).

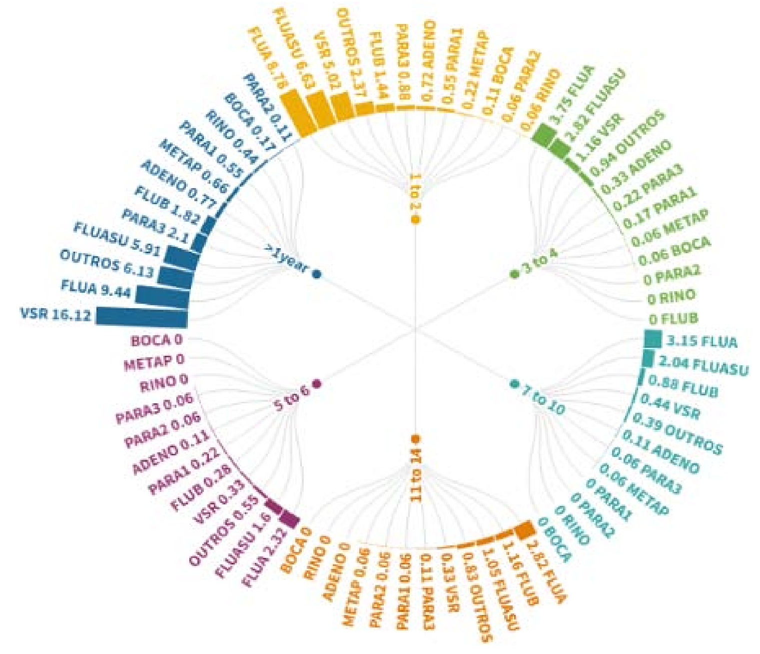

Figure 6: Death per SARI/SARS-causing virus year 2013 to 2019, Brazil.

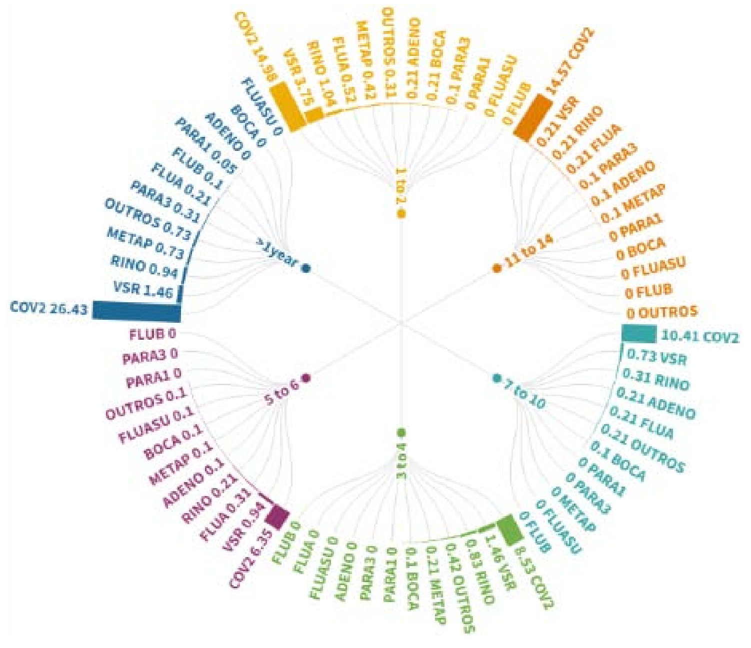

Figure 7: Death per SRAG-causing virus year 2020 to 2021, Brazil.

When the years 2020 and 2021 were evaluated, the average number of deaths was similar (3%, 2020, 1.8% 2021). COVID-19 was the most prevalent cause of death in all age groups studied (81.27%) followed by RSV (8.55%) and Rhinovirus which was 3.51%. The highest incidence rate of deaths continues to be children under 01 years of age. In this period, SARI cases with death outcomes caused by influenza A and influenza B subtype viruses account for only 1.35% of cases, a large decline when compared to previous years. Note that the pandemic period, 2020 and 2021, dates to the viral profile of the prevalence of deaths from SARI, discontinuing what had been previously observed. Prevalence and incidence data of deaths considering the virus causing SARI and SARS are shown in (Figure 6 and Figure 7).

Discussion

Severe acute respiratory infection is the leading cause of morbidity and mortality in pediatric patients worldwide and imposes intense pressure on health services [20]. This data compilation demonstrates Brazil's surveillance of SARI and SARS cases and the importance that this comorbidity represents for the health of the Brazilian population. With the emergence of the New Corona virus pandemic, the case number doubled, and in the first half of 2021, the number of cases was like the entire year of 2020. It was found that, in the absence of the New Coronavirus pandemic, the number of SARI cases in children and adolescents aged 0 to 14 years, would have followed the pattern of previous years, approximately twenty thousand cases annually.

In 2016, there was a significant increase in SARI cases in Brazil and according to the National Confederation of Municipalities of Brazil, the H1N1 virus caused the highest number of deaths since the arrival of this virus in 2009, mainly because the virus started circulating ahead of schedule, with the population not being immunized and causing many deaths. The influenza A rate was 38% for all viruses detected. Experts deduce that this anticipation of the virus may be due to the increase in international travel to northern countries, where the virus circulated or to climatic factors. There were also several cases of SARI due to other types of influenza [21-22]. According to the Centers for Disease Control and Prevention (CDC), influenza A (H1N1) pdm09 viruses were the viruses that circulated most in the United States during the 2015-2106 seasons [23].

Among the different pathogens causing SARI, the RSV was the most prevalent throughout the period from 2013 to 2021 (50%), except for 2016 where there was an outbreak of influenza A (H1N1) pdm09, as described above. In general, cases of SARI caused by influenza A and influenza B viruses show wide variations over the years, different from parainfluenza viruses 1,2,3 and 4 that appear every year, but at a much lower rate of contamination, and in the year 2020 with the pandemic, COVID-19 is responsible for 61.0% of identified SARS cases, and in this period the RSV has a rate of 8.6%. In the first half of 2021, cases of COVID-19 decreased and 37% of SARI cases were due to respiratory syncytial virus.

As reported in previous studies, RSV affects 12% to 63% of children with SARI hospitalized in Western countries, a number very similar to that found in this study (22.7% of cases of hospitalized children with SARI due to RSV). In two countries in South America, Ecuador and Colombia, the RSV rate found was 39.2% and 33.8%, respectively [20,24-25]. Worldwide, RSV is responsible for most respiratory tract infections in infants and young children, generating high public health costs, with approximately 3.4 million children under 5 years of age with this infection requiring hospitalization in around the world [26].

In Brazil, since 2009, surveillance of Severe Acute Respiratory Infection has been carried out in Brazil, due to the Influenza A (H1N1) pdm09 pandemic [16]. The cases of SARI caused by Influenza-A subtype and influenza-b viruses, show great variation over the period, with the average of each being 8.6%, 11.4%, and 18.25%, respectively. In another study, a rate of 12.1% in total cases of SARI due to influenza, and 12% of children under 05 years of age, hospitalized with SARI, showed that influenza A (H3N2) was the most prevalent type and that it contributes to the hospitalization of children. A survey of 347 children aged 0 to 15 years with SARI showed that the influenza virus was present in 9.8% of cases and the respiratory viruses were responsible for the high rate of hospitalization in the studied population [27-29].

Rhinovirus emerged from 2019 with a rate of 7% and 2020 and 2021 was 10.8%. The rates of this virus found in the literature were 11%, 77%, 36%, and 33.5% [30-33]. We believe that the index of this virus found in this study does not represent the real situation and is due to the type of test used to detect it. Many viruses that cause respiratory tract infection are not identified at a rate of 32-39%, and this is significantly due to the sensitivity of the diagnostic test used, the type and location of the sample and the geographic area of the study [34].

The monthly distribution of SARI cases due to respiratory viruses followed an annual seasonality, increasing from April to June, demonstrating the same seasonality from 2013 to 2019, but in 2020 the peak was in July, two months ahead of the seasonal peak. In 2021, the peak was in May, like the years before the pandemic. Among seasonal epidemics, it is possible to classify three groups of respiratory viruses, the influenza virus, the HCoVs, and the RSV which are detected with high peaks in winter and are called winter viruses. Adenovirus, HBoV, parainfluenza virus, hMPV, and human rhinovirus can be detected throughout the year. Epidemics caused by viruses, such as the SARS-CoV and the newly emerging SARS-CoV-2, occur during the winter months [35].

Surveillance for cases of SARI due to influenza is important, as it allows identifying the factors that led to hospitalization, and with this, monitoring how health agencies use prevention, treatment, and vaccination strategies, and how much this virus affects the hospitalized children. Influenza produces a severe respiratory infection that causes high morbidity and affects all ages but can be avoided with vaccination [28].

In 2020, with the onset of the pandemic, the pattern of cases of SARI by virus is very different from that observed in previous years, SARS-CoV-2 was responsible for 61.0% of the identified cases, the RSV significantly decreased. In the first semester of 2021, there is a decrease in cases caused by SARS-CoV-2, and the circulation of the respiratory syncytial virus increases again.

A study comparing children with SARI due to RSV before and after the measures of social isolation because of COVID-19, found a 70% decrease in the number of SARI cases, a number very similar to that found in Brazil, in the same period [36]. There was a decline in SARI cases during the pandemic and a decrease in the circulation of seasonal respiratory viruses, including the influenza virus as well. In the northern hemisphere, the indicators of influenza circulation also decreased, with the spread of SARS-CoV-2, and this decrease was attributed to changes in the health routine in search of respiratory diseases, as well as in the circulation of the influenza virus, due to wide implementation of measures to mitigate the transmission of SARS-CoV-2 [37].

In New Zealand, COVID-19 containment measures appear to have decimated transmission of seasonal RSV and influenza viruses in infants, and this is believed to be due to international border controls, mandatory 14-day isolation of arriving passengers, which limits the entry of seasonal viruses in the country, as well as social distancing and hygiene measures in the population [38]. To prevent the spread of COVID-19, since the beginning of the pandemic, most countries in the world have used community mitigation strategies for there were no available vaccines and assertive medical interventions. Community mitigation strategies include hand hygiene, wearing face masks, social distancing and crowding [39].

Mitigation strategies were implemented in stages and in different ways by countries and the results of controlling the spread of the virus also depended on socioeconomic, cultural, and health authorities in each country to implement those procedures. To be effective, these measures need to establish social protection and support policies for vulnerable individuals, so that they can sustain themselves during the restrictions. Brazil is a country with great social inequality and a minimum income guarantee was necessary so that most of the unemployed population could adhere to measures of social distancing [40].

In the period from 2013 to 2019, the influenza A virus caused most deaths in all age groups (30.26%), followed by RSV (23.4%), but when evaluated only children under 1 year of age, RSV was the one that most led to death (16.12%). In 2020 and 2021 the profile was different, the mortality of children with respiratory infection was due to COVID-19 (81.27%) and the rates for the other viruses decreased significantly, 8.55% for RSV and 1.35% influenza A. Children under 1 year of age had a higher rate of deaths.

Other studies that describe that the influenza virus and RSV are responsible for the deaths of children with SARI, demonstrated that the average death from influenza in winter is 22% and RSV is 28%, data a little different from that found in this research, where deaths from SARI were due to influenza when all ages were analyzed. However, when only children under 01 years of age were analyzed, the data were the same as those of the authors, where RSV is the main cause of death in children of this age group. RSV is well known for causing an excessive mortality rate in young children and the elderly population in winter [41-42].

The SARI mortality profile due to respiratory viruses changed with the COVID-19 pandemic, being extremely higher, almost decimating the other viruses (influenza and RSV). Previous studies have described a mortality rate in children aged 0-9 years from COVID-19 in China (0.9%), South Korea (1.0%), and Italy, Lombardy region (0.4%), noting that children with SARS-CoV-2 did not have severe disease. A 40% rate of children under 10 years of age who died of COVID-19 has been described, but further studies are needed to understand the role of SARS-CoV-2 mechanisms that lead children to death. In Ontario (CA) there were no confirmed deaths of children aged 0-13 years due to COVID-19 [43-45].

In conclusion, the cases of SARI in children aged 0 to 14 years, from 2013 to 2019 maintained a pattern, where there was a high prevalence of RSV, followed by influenza, except for 2016, with an outbreak of H1N1 pdm09. However, in 2020 and 2021 SARS-CoV-2 was the most prevalent, almost decimating the other viruses, which we believe was due to mitigation measures to control the pandemic. Children under 1 year of age, in all studied variables, were the most affected. SARI cases had seasonality between the months of April to June, which are winter months in Brazil. In the pandemic, the peak of seasonality in 2020 was in July and in 2021 it was in May. During all the years studied, influenza was the main cause of death from SARI, but RSV was more prevalent in children under 1 year of age. However, during the pandemic, COVID-19 predominated in cases of SARS.

Conclusion

We believe that these changes in the pandemic years, both at the peak of seasonality and the prevalence of viruses, are due to Brazil's mitigation strategy to contain COVID-19.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

The authors contributed equally to this work.

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