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Prevalence of respiratory viruses in children in Northeast Brazil: The scenario before the COVID-19 pandemic

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ABSTRACT

Objectives: To investigate the prevalence of nine respiratory viruses and their clinical characteristics in children aged up to 5 years old in the state of Sergipe, Northeast of Brazil in the pre–COVID-19 pandemic period.
Methods: Children with suspected influenza virus infection were included in the study. Clinical samples were screened using real-time quantitative polymerase chain reaction for the diagnosis of adenovirus, parainfluenza (PIV)1, PIV2, PIV3, and human metapneumovirus. In addition, data were collected for influenza A viruses (H1N1 and H3N2), influenza B virus, and respiratory syncytial virus.
Results: From January 2018 to December 2019, 1081 samples were selected. Of these, 64.1% (n = 693) were positive for at least one of the nine screened respiratory viruses. The most prevalent etiologic agent in the study period was respiratory syncytial virus, detected in 31.8% (344 of 1081) of cases, and the least prevalent was the influenza B virus, detected in 0.6% (six of 1081) of cases. Single infections were found in 85.5% (594 of 693) of the cases, whereas 14.4% (100 of 693) had coinfections. There was no correlation when comparing reported signs and symptoms with real-time quantitative polymerase chain reaction positivity and the type of virus detected. The study highlights the importance of monitoring the etiological agents responsible for respiratory infections in children before the COVID-19 pandemic.

Introduction

Acute respiratory infections (ARIs) are the main causes of morbidity and mortality in children under 5 years of age in low-resource countries [1]. It is estimated that around 3.4 million children under 5 years of age are affected by a serious illness and 91% occur in low-resource countries [2,3]. In Brazil, the circulation of respiratory viruses occurs throughout the year, with higher incidences between March and September, which marks the end of summer and beginning of winter season [4]. In the child health context, respiratory syncytial virus (RSV) is the main causative agent of ARI, accounting for 34 million cases per year globally, with more than 90% of deaths occurring in low- and medium-income countries [5]. Other viruses, such as adenovirus (AdV), parainfluenza (PIV) 1-3, and human metapneumovirus (hMPV) are also significant causes of respiratory infections in children [6,7]. In March 2020, a state of pandemic was declared in Brazil, caused by the SARS-CoV-2 virus, but it did not represent a major risk for children because they usually presented milder or asymptomatic forms [8,9]. During the pandemic period, surveillance systems redirected their attention to monitor mainly the SARS-CoV-2 cases. Studies have demonstrated that direct or immune-mediated virus-virus interactions can occur, which can modify the dynamics of annual periods of outbreaks of other respiratory viruses [10]. To better understand these interactions, it is necessary to assess how these viruses present themselves in the epidemiological environment. Therefore, the objective of this study was to identify the pre-pandemic prevalence of nine viruses associated with respiratory infections and their clinical characteristics in children up to 5 years of age with flu-like symptoms in the state of Sergipe, Northeastern Brazil.

Materials and methods

Study population

Up to 1081 respiratory samples, including nasopharyngeal and oropharyngeal swabs, were collected from children under 5 years old according to the criteria established by the national influenza

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surveillance program of the Brazilian Ministry of Helath in the Sergipe state and sent to the Central Public Health Laboratory of the state of Sergipe (LACEN-SE). Sergipe state has four sentinel units: Hospital Governador João Alves Filho, São Lucas Hospital, Santa Isabel Hospital, and Hospital Municipal Zona Sul de Fernando Franco. The sampling was collected from January 2018 and December 2019 from severe ARIs (SARI) cases and influenza-like illness (ILI) cases detected in these sentinel units. ILI cases were defined as individuals with fever, even if referred, accompanied by a cough or sore throat, and SARI cases are hospitalized individuals with ILI and presenting with dyspnea and respiratory distress [11].

Viral RNA extraction and quantitative polymerase chain reaction (qPCR) screening for other respiratory virus detection

LACEN-SE routinely tests for influenza A viruses subtype H1N1 (FluA/H1N1), influenza A viruses subtype H3N2 (FluA/H3N2), influenza B viruses (FluBs), and RSV. Viral RNA was extracted from 140 µL of sample using the QIAmp viral RNA mini kit (QIAGEN, Hilden, Germany) and eluted in 80 µL nuclease-free water, according to the manufacturer's manual. Real-time reverse transcription–PCR target to detect Influenza A (H1 and H3 subtypes), influenza B (B/Victoria and B/Yamagata lineages) and RSV using primers and probes specificity were carried out with 5 µL of extracted RNA for target [12,13]. After screening for these four viruses, all samples, regardless of the result of the first screening, were tested for five other respiratory viruses: AdV, PIV1, PIV2, PIV3 and hMPV. These were selected due to the availability of these assays by the National Influenza Program of the Brazilian [14,15]. RNA was obtained using the Bio Gene® Viral RNA/DNA extraction kit (Quibasa-Bioclin, Belo Horizonte, Brazil). Virus detection was performed by real-time qPCR using primers and specific probes, following the protocol described by Zhou et al. [16]. The amplification reactions were performed using the GoTaq RT-qPCR One-Step System (Promega Corporation, WI, USA), with a final volume of 25 µL, containing 12.5 µL GoTaq qPCR Master Mix (2×), 0.1 mM of each primer, 0.1 mM µL of probe, 0.5 µL of reverse transcriptase qPCR enzyme mix, 5 µL viral RNA, and RNase-free water to complete the volume. Cycling was performed with the activation of the reverse transcriptase enzyme for 25 minutes at 45°C, followed by initial denaturation at 94°C for 2 minutes and 45 cycles of denaturation at 95°C for 15 seconds, followed by 30 seconds at 55°C for hybridization and extension. In all reactions, positive and negative controls were used. The results were analyzed with the Applied Biosystems 7500 Real-Time PCR Software v 2.0.5 (Applied Biosystems, MA, USA) based on amplification curves with sigmoidal shape and considered detectable when presenting a cycle threshold ≤39.

Clinical and epidemiological data

The children's clinical data were obtained from the ILI and SARI case notification forms, provided by the state Secretary of Health. The following demographic, medical, and healthcare data were collected from these records: sex, age, municipality of residence, month of notification, type of notification, health unit, associated risk factors (pneumopathies, heart diseases, Down syndrome, HIV/AIDS, and others), use of antivirals, hospitalization in intensive care unit, and chest X-ray results. In addition, the following clinical information was also obtained: presence of fever, cough, runny nose, myalgia, sore throat, dyspnea, respiratory distress, and O_2 saturation <95%.

Statistical analysis

Statistical data were processed using the R version 4.0.0 software and the significance level adopted was 5%. An exploratory data analysis was performed with the description of the simple and relative frequencies. The relationships between some variables were explored, using the statistics indicated for independent samples, namely, the Pearson chi-square test and Fisher's exact test.

Ethical considerations

This study was approved by the Ethics Committee in Research Involving Human Beings of the Federal University of Sergipe under the number CAEE 25974119.0.0000.5546.

Results

From January 2018 to December 2019, 1081 clinical samples from children under 5 years of age were analyzed for the presence of nine respiratory viruses to identify the etiology of symptoms of ILI or SARIs. The results showed that 64.1% (n = 693) of the study sample were positive for at least one of the viruses. Analyzing the sex of infected children, 57.4% (n = 398) of cases were male and 42.6% (n = 295) were female, with no statistical difference between the sexes of the children ($P = 0.08$), as seen in Figure 1. During the study period, the most prevalent virus detected was RSV, with a detection rate of 31.8% (344 of 1081). In addition, there was also a high prevalence of AdV, present in 15.6% (169 of 1081) of the study sample, hMPV with a prevalence of 7.3% (79 of 1081), FluA/H1N1 6.9% (75 of 1081), and PIV3 6.3% (69 of 1081). The other viruses were detected with lower prevalence are the following: PIV1 2.8% (31 of 1081), FluA/H3N2 1.4% (16 of 1081), PIV2 0.9% (10 of 1081), and FluB 0.5% (six of 1081), as shown in Figure 2. In the study, the circulation of respiratory viruses occurred throughout the year in 2018 and in 2019, with a higher incidence between April and July, comprising the autumn and winter seasons. In autumn, 53.6% (369 of 693) of the positive cases were recorded and 21.8% (151 of 693) during the winter, with a statistical difference between seasons ($P = 0.00$). The peaks of viral circulation occurred in April and June for 2018 and 2019, respectively, both driven by RSV. For a better understanding of viral co-circulation, all cases were analyzed for the presence of one or more viruses. Single infections were found in 85.59% (594 of 693) of the children, dual infections in 13.40% (93 of 693) and triple infections in 1.01% (seven of 693) (Figure 3). Among the single infections, RSV had the highest rate of single infections, with less than 20% of mixed infections (double or triple). Respiratory infections caused by FluA/H3N2 and PIV2, in addition to their low prevalence (Figure 2), had a high rate of mixed infection, with 50% of FluA/H3N2 and 40% of mixed PIV2 cases (30% double and 10% triple). In the study, different interactions between the viruses were identified, all of which were detected in dual and/or triple infections, except FluB and FluA/H3N2, which were not detected in triple infections (Figure 3). Comparing the symptoms of the children infected with at least one of the nine respiratory viruses, statistical differences were observed. We observed that SARI was more frequent, 54.4% (377 of 693) in children with a positive viral diagnosis ($P = 0.000$) than in children with an unknown etiologic agent. However, cases of ILI were more frequent in children with a negative viral diagnosis, being 63.9% (248 of 1081) of the cases. Analyzing the clinical characteristics, the most prevalent symptoms in the infected group were dyspnea 59.5% (412 of 693), respiratory discomfort 48.1% (333 of 693), and O_2 saturation <95% 29.4% (204 of 693). However, other symptoms were found in this study, such as cough, fever, runny nose, and sore throat, as specified in Table 1. In addition, risk factors were also observed in children infected with respiratory viruses. The most common were prematurity in 3.1% of the children (34 of 1081), cardiac disease in 2.1% (23 of 1081), Down syndrome in 0.9% (10 of 1081), asthma in 1.3% (15 of 1081), and other risk factors in 10.2% (111 of 1081). However, there was no statistical difference between positive and negative cases regarding these risk factors. During the treatment, the antiviral oseltamivir was prescribed to 27.7% (192 of 693) of infected patients, which was statistically significant ($P = 0.000$) compared with negative cases. Regarding admission to the intensive care unit, 17.9%

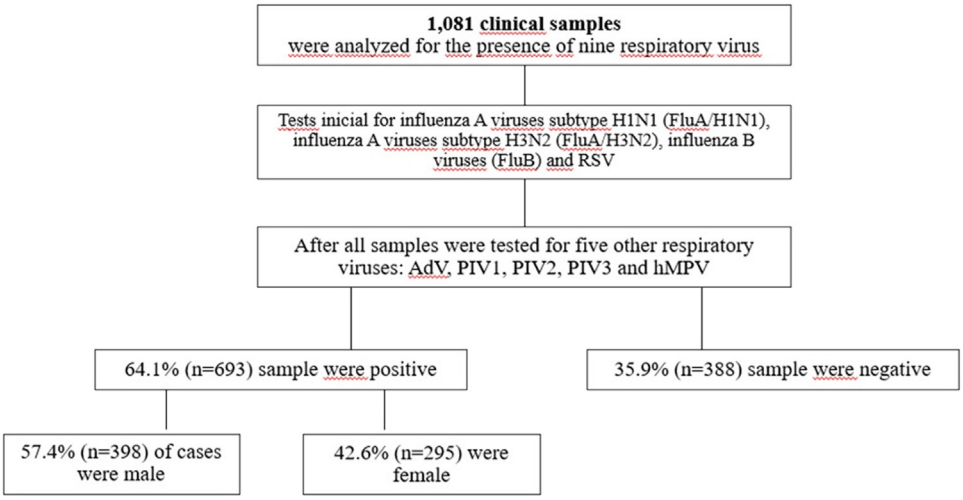

Figure 1. Detailed flowchart of study organization, including tests performed and sample number.
AdV, adenovirus; hMPV, human metapneumovirus; PIV, parainfluenza.

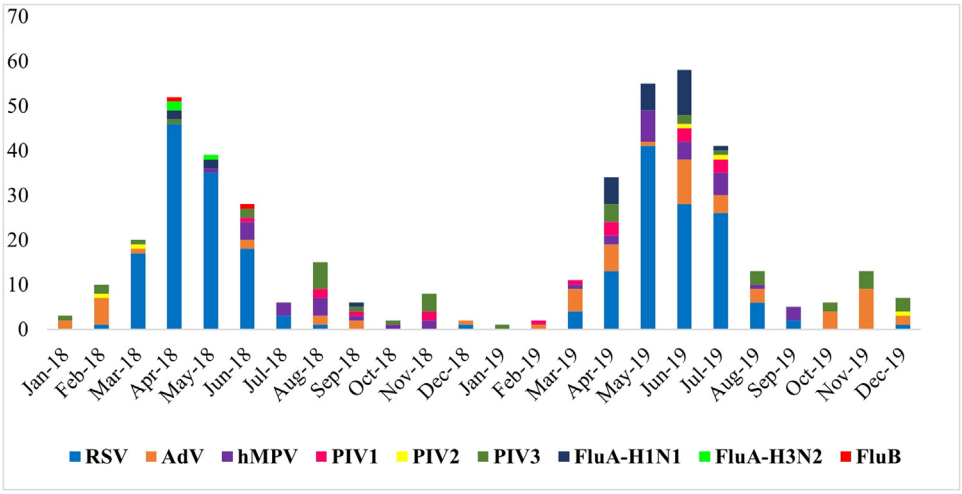

Figure 2. Distribution of positive cases of respiratory viruses in children up to 5 years old in the state of Sergipe between 2018 and 2019.
AdV, adenovirus; hMPV, human metapneumovirus; PIV, parainfluenza; RSV, respiratory syncytial virus.

(124 of 693) of children diagnosed with a positive virus were admitted, with no statistical difference ($P = 0.20$) with uninfected children, as shown in Table 1.

Discussion

Infectious diseases are the main health problems in pediatrics in the world, and there are a wide variety of epidemic-prone viruses that are often difficult to differentiate based on clinical presentation. The surveillance of respiratory viruses in the state of Sergipe showed that most cases reported with respiratory symptoms had at least one virus as the etiologic agent. The positivity of 64.1% for at least one of the nine screened viruses is similar to other Brazilian studies [17,18], mainly related to the high prevalence of RSV, which was identified in 31.8% of our cases. In the state of São Paulo, in a screening for six respiratory viruses in children, the highest prevalence was found for RSV (24.1%), followed by hMPV (17.8%) [19]. These findings emphasize the high circulation of RSV and hMPV in different regions of the country, even in different years, which shows the importance of constant monitoring of the circulation of these viruses over the years. We found a variable viral circulation during the 2 years analyzed. Although positive cases were present throughout the year, the period from April to June in 2018 and 2019 had the highest number of cases. RSV was detected for most of the year, with a higher incidence between March and June 2018 and from April to July 2019, presenting as the main etiological agent of respiratory diseases in children before the epidemic period. AdV and PIV3 continued to circulate throughout the study period and appear to be the main viruses outside the 2018 seasonal period, although their prevalence remained until the end of 2019. This is possible due to the way in which all respiratory viruses are transmitted, which can be either through the spread of droplets or through contact with contaminated surfaces or objects. In addition, it is possible to be an asymptomatic carrier of an AdV, which has a relatively long incubation period that favors the continuity of the transmission chain [20,21]. Despite the low prevalence, PIV1 was detected among the months of lowest viral circulation in 2018, between June and November. In 2019, PIV1 was detected from the beginning of the year and remained present in the months of high virus circulation between February and July. Among the PIVs, PIV2 was the least detected, with cases identified between February and March 2018 and in June, July, and December in 2019. hMPV had similar seasonality to RSV in 2018, and, in 2019, it was found between June and November. An increase in FluA/H1N1 circulation can also be observed in 2018. Although RSV was the most prevalent virus during the 2 years of analysis, there were significant differences between its prevalence and that of other respiratory viruses from 1 year to the next. Apparently, the decrease in RSV in 2019 seemed to favor a greater diversity of the other viruses identified, which were present only in non-epidemic months, such as hMPV, AdV, PIV1, and PIV2. This may be a result of decreased susceptibility to RSV due to naturally acquired immunity in previous years. It is important to highlight that the interactions between two or more pathogens in a single host are complex and multifactorial [10]. Screenings performed in different countries using real-time qPCR

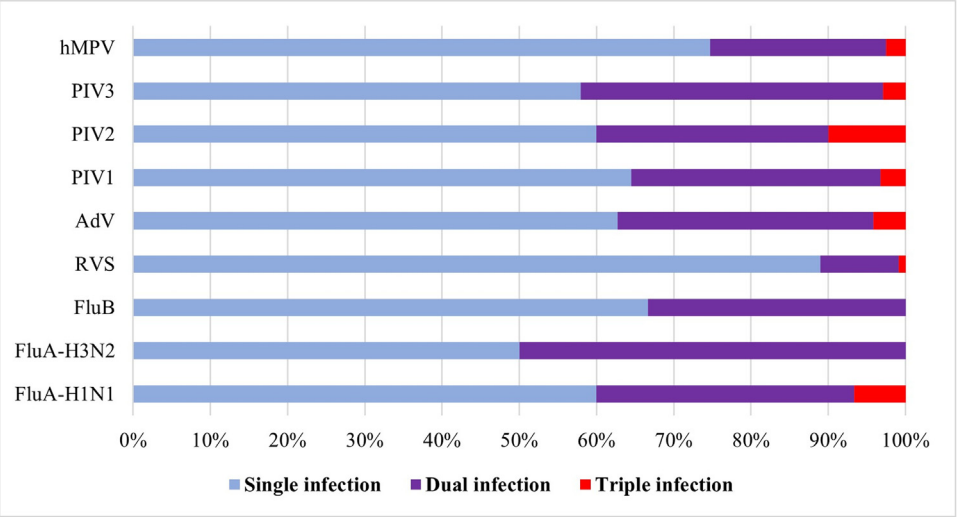

Figure 3. Proportion of viruses found in single, double, and triple infections in children up to 5 years of age in the state of Sergipe between 2018 and 2019.
AdV, adenovirus; hMPV, human metapneumovirus; PIV, parainfluenza; RSV, respiratory syncytial virus.

Table 1
Analysis of the clinical characteristics of children up to 5 years old in the state of Sergipe between 2018 and 2019, with symptoms of respiratory infection and qPCR diagnosis for respiratory viruses.

Characteristics	n (positive cases)	%	n (negative cases)	%	*P*-value[a]
Notification type					
GS	316	45.6	248	63.9	**0.000**
SARS	377	54.4	140	36.1	
Signs and symptoms					
Fever	596	86.0	353	91.0	**0.021**
Cough	662	95.5	372	95.9	0.908
Sore throat	92	13.3	76	19.6	**0.007**
Coryza	172	24.8	141	36.3	**0.000**
Dyspnea	412	59.5	170	43.8	**0.000**
Respiratory discomfort	333	48.1	122	31.4	**0.000**
Saturation O_2 <95%	204	29.4	83	21.4	**0.005**
Myalgia	9	1.3	3	0.8	0.553
Others	147	21.2	82	21.1	1.000
Radiography chest					
With change	269	38.8	95	24.5	**0.000**
No change	424	61.2	293	75.5	
Risk factors					
Asthma	9	1.3	6	1.5	0.949
Prematurity	26	3.8	8	2.1	0.178
Down syndrome	6	0.9	4	1.0	0.752
Heart disease	17	2.5	6	1.5	0.440
Others	77	11.1	34	8.8	0.264
Use of antiviral					
Yes	192	27.7	68	17.5	**0.000**
No	500	72.3	320	70.4	
Admission of intensive care unit					
Yes	124	17.9	57	14.7	0.204
No	569	82.1	331	85.3	

qPCR, quantitative polymerase chain reaction
[a] ***P*-value:** Pearson chi-square test and Fisher's exact test.

report different percentages of viral respiratory prevalence (in Bulgaria [78.1%] [22], China [14.55%] [23], Spain [75.2%] [24], and Turkey [58.7%]) [25]. This variation may occur due to the quantity and quality of the screened samples, different climatic and geographic factors, and the sociodemographic characteristics of the population studied. However, most of these studies are limited to assessing the prevalence of viral respiratory infections in hospitalized children at specific times of the year, with underreporting of the prevalence of virus circulation in non-hospitalized children. In our study, 64% of the tested samples were positive for at least one of the viruses analyzed. This prevalence is notably high, especially considering that these samples were collected throughout the year. These findings underscore the urgent need for preventive and transmission control measures to mitigate the current scenario. In hospitalized children in Hubei Province, Central China, reported symptoms such as fever, cough, and other symptoms showed statistical differences between infected, uninfected, or co-infected children. In addition, also in China, most children with fever were hospitalized and completed a course of antibiotics without an accurate diagnosis of bacterial infection [26,27]. It is important to highlight that RSV was the virus with the highest circulation in this study and was also present mainly in single infections, particularly, impacting children during the seasonal period between March and July. These findings show that this virus seems to have high infectivity, considering its higher occurrence in single infections, and underscores the urgent need for preventive interventions to alleviate the burden of RSV-related hospitalizations and health care strain. Recent advances in RSV prevention, such as maternal vaccines

and monoclonal antibodies, offer promising tools to mitigate this high burden [28,29]. One notable development is the bivalent RSV prefusion F protein-based vaccine, which has demonstrated over 80% efficacy in preventing severe RSV-associated lower respiratory tract illness in infants when administered during pregnancy [28,30]. In a context such as Brazil, where RSV prevalence is high, the introduction of this vaccine could significantly reduce health care burdens, particularly, during peak RSV seasons. In addition, monoclonal antibodies, such as nirsevimab, recently approved in Europe for infant protection, show great promise in extending passive immunity to all infants during their first RSV season [29,30]. The implementation of these strategies is crucial for reducing RSV-related morbidity and mortality, especially as viral interactions become increasingly complex. As highlighted in our findings, despite the low frequency of co-infections between RSV and other respiratory viruses, studies demonstrate an increase in the severity of infection with RSV in situations of coinfection [31–33]. According to Antalis et al. [32], children co-infected with respiratory viruses have a higher risk of mortality than singularly infected children. At peak times of infection, cases of viral coinfections occurred more frequently. Viruses associated with co-infections can interact within the host and modify their form of replication, the immune system response, and the pathogenesis of the disease and even cause a secondary bacterial infection [34]. Understanding the interplay between RSV and other pathogens is essential for informed public health planning, especially considering the ongoing challenges posed by respiratory viruses in a post–COVID-19 environment. Thus, robust surveillance systems are imperative to monitor these dynamics and guide timely interventions aimed at protecting vulnerable populations. Every year in Brazil, children require medical treatment for respiratory symptoms, especially in autumn and winter. Viral respiratory infections are common, and, together with the many other infectious diseases that are endemic in our region, put a great deal of pressure on the public health system. For a better understanding of the clinical picture associated with ARIs, we compared the symptoms presented by children with the identified viruses. In this study, we compared the signs and symptoms reported with the type of virus detected and observed that dyspnea, respiratory discomfort, and O_2 saturation <95% were significantly higher in positive cases. Surprisingly, some significant symptoms, such as coryza, fever, and sore throat, occurred in children with a negative viral diagnosis, underlying the limitations of relying solely on clinical symptoms for diagnosis and treatment. However, it is important to emphasize that all the samples from children with suspected respiratory infection due to the presence of indicative symptoms were sent to LACEN/SE which performed tests for nine respiratory viruses. Importantly, when we analyzed the correlation between reported symptoms and qPCR positivity for the detected viruses, no significant correlation was found. This reinforces the notion that a clinical diagnosis cannot solely depend on the presented symptoms. Currently, it is necessary to consider the potential risk of clinical manifestations during infection by these viruses in a co-circulating environment with SARS-CoV-2. It has been reported that patients co-infected with influenza and SARS-CoV-2 can progress from mild to moderate infection and, in some cases, require the use of ventilatory support. In these cases, the severity of the patient's clinical condition varies according to the type of influenza virus, with coinfection between SARS-CoV-2 and FluB reported to be related to the most severe cases of infection [31–36]. Therefore, surveillance of other viruses post–COVID-19 pandemic is important to identify what effect the emergence of this virus will have in the co-circulation environment with other known pathogens. In addition, we need to consider that the epidemiological environment may change due to the administration of vaccines against COVID-19, thus opening a niche for other viruses to cause outbreaks.

Conclusion

This study showed that most reported cases of respiratory infections in children had at least one virus as the etiologic agent and that RSV was the most prevalent respiratory viral infection in children in the state of Sergipe, Northeastern Brazil in the 2 years before the beginning of the COVID-19 pandemic. In addition, a seasonal period was identified from April to July. Moreover, all viruses identified in this study were also found in mixed infections. Comparing the reported signs and symptoms with qPCR positivity in relation to the type of virus detected, no correlations were found. The scenario in respect of the epidemiology of respiratory viruses, including those in children, is constantly evolving with the emergence of variants of concern, as was shown by the COVID-19 pandemic. Our findings contribute valuable data on the diversity and seasonality of viral respiratory infections, which is critical for public health planning and preparedness. The absence of clear clinical correlations between symptoms and specific viruses underscores the limitations of symptom-based diagnoses and the need for continuous, broad viral surveillance. Understanding the circulating pathogens, their timing, and the populations they affect can inform the strategic introduction of vaccines, such as the forthcoming RSV vaccines, and the use of monoclonal antibodies, which could significantly reduce RSV-related morbidity and health care burden in Brazil.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contribution

Rafaela W.F. Santos: conceptualization, methodology, data collection, data analysis, validation, investigation, data curation, writing - original draft preparation. Antoniele S. Pimentel: validation, investigation, data curation, writing- original draft preparation. Myrela C.S. Jesus: data curation, visualization. Cliomar Santos: conceptualization, formal analysis, data curation. Jose R.S. Silva: formal analysis, data curation, visualization. Ricardo L.D. Machado: validation, data curation, visualization. Luciane M. Storti-Melo: conceptualization, validation, formal analysis, data curation, resources, supervision, project administration, funding acquisition. All authors: writing-review & editing.

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