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Original article

Severe viral lower respiratory tract infections in Brazilian children: Clinical features of a national cohort

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ABSTRACT

Background: The accurate etiological diagnosis of lower respiratory tract infections (LRTI) is essential for their effective clinical management. The extensive use of molecular methods during the COVID-19 pandemic has enabled massive data acquisition on viral lower respiratory tract infections. The current study aims to identify clinical features associated with eight viral agents among children presenting severe LRTI.
Methods: retrospective cohort study of data from the Brazilian Influenza Epidemiological Surveillance Information System. Patients under 20 years-old who had severe LRTI with etiological confirmation through RT-PCR between 2020 and 2022 were included. Binary logistic regressions were used to examine associations between pathogens and symptoms.
Results: 60,657 cases were assessed. The main viral agents detected were Sars-CoV-2 (COV2) (41.2%), Respiratory Syncytial Virus (29.1%), Human Rhinovirus (HRV) (12.1%), and Influenza (FLU) (5.5%). A general mortality rate of 4.3% was observed. The multivariate analysis evidenced that COV2 less likely presented with cough (OR: 0.34; 95%CI: 0.32–0.36), respiratory discomfort (Adjusted Odds Ratio (aOR): 0.61; 95%Confidence Interval (CI): 0.59–0.64), and desaturation (aOR: 0.71; 95%CI: 0.69–0.75). RSV strongly associated with cough (aOR: 2.59; 95%CI: 2.45–2.75) and respiratory discomfort (aOR: 1.54; 95%CI: 1.46–1.62), whereas FLU was linked to fever (aOR: 2.27; 95%CI: 2.06–2.50) and sore throat (aOR: 1.48; 95%CI: 1.34–1.64).
Conclusions: The viral agents responsible for severe LRTI have distinct associations with clinical features in children.

Introduction

Acute respiratory infections (ARIs) are common in children, with most experiencing three to six episodes annually regardless of country or economic situation [1]. These infections can range from mild upper respiratory illness to lower respiratory tract infections (LRTI), which require special attention, as it progresses in severity. LRTIs ranks among the leading causes of death in children aged zero to nine years worldwide [2]. In Brazil, they significantly contribute to the overall burden of respiratory diseases in pediatric populations.

Respiratory viruses are a common cause of LRTIs in children, and the most associated viruses include respiratory syncytial virus (RSV), influenza (FLU), parainfluenza virus (PIV), human metapneumovirus (HMPV), and human rhinovirus (HRV) [3]. However, the emergence of SARS-CoV-2 (COV2) in 2020 introduced a new etiological agent to consider in the diagnosis of LRTI. Molecular detection methods, such as real-time polymerase chain reaction assays (RT-PCR), are often employed for accurate diagnosis [4]. During the COVID-19 pandemic,

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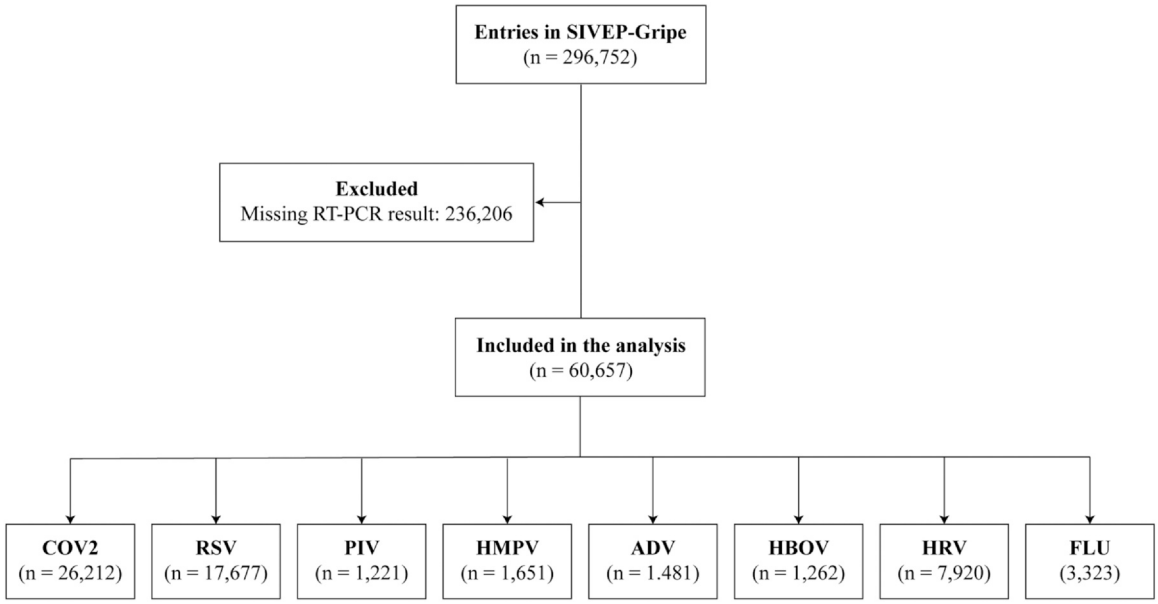

Fig. 1. Flowchart of the study. Abbreviations: SARS-CoV-2 (COV2), Respiratory Syncytial Virus (RSV), Parainfluenza Virus (PIV), Human metapneumovirus (HMPV), Adenovirus (ADV), Human Bocavirus (HBOV), Human Rhinovirus (HRV), Influenza (FLU).

the widespread use of RT-PCR has facilitated the monitoring of disease burden and the evaluation of control measures, such as vaccine introduction and the implementation of respiratory precautions. it has also enabled targeted therapeutic management for symptomatic infections [5–7].

In Brazil, the monitoring of viral ARIs has been a national public health policy since 2009 [8]. The extensive use of RT-PCR during the COVID-19 pandemic has enabled massive data acquisition on the burden of severe LRTI caused by various viruses. This information is important for the development of control and prevention strategies by health authorities [9]. Nonetheless, a need remains for the comprehensively characterization of severe LRTIs to guide evidence-based clinical practices and public health interventions [10–12]. The aim of this study is to evaluate severe cases of viral respiratory infections among children reported in a national surveillance system for influenza-like illness during the COVID-19 pandemic in Brazil and identify the main virus-specific clinical characteristics. The hypothesis of the study was that there are clinical and epidemiological differences between the viral agents causing severe LRTI.

Materials and methods

Study design

This retrospective cohort study used public data made available by the Brazilian Ministry of Health. All cases of severe viral LRTI in individuals up to 19 years of age with laboratory confirmation of the etiological agent were analyzed from February 21, 2020, to August 21, 2022, according to data availability. These cases were registered in the SIVEP-Gripe (Influenza Surveillance Epidemiological System) database.

Data source

The Influenza Surveillance Epidemiological System was implemented in response to the Influenza A(H1N1) outbreak in 2009 and was designed to monitor and track cases of LRTIs to assist in the control and prevention of the disease. Within this framework, notification of individuals hospitalized with severe LRTIs is mandatory, regardless of whether they are in a public or private healthcare institution in Brazil. Doctors and nurses are responsible for completing standardized reporting forms when a diagnosis of LRTI is suspected. These forms are updated as significant patient development occur (laboratory confirmation, hospitalization, ICU admission, discharge, or death). In the system, each patient receives a unique identification code that is updated as new notifications are made, thereby allowing the longitudinal evaluation of cases [13].

Variables definitions

Severe viral LRTI was defined as a flu-like syndrome with dyspnea, or persistent pressure in the chest, or O2 saturation less than 95% in room air, or cyanosis. In children, additional markers include nasal flaring, cyanosis, intercostal indrawing, dehydration and lack of appetite [13]. For each case, self-reported symptoms, comorbidities, and sociodemographic data were collected. Dates of hospital and intensive care unit (ICU) admission, need for ventilatory support, and clinical outcome were also recorded. All variables were defined according to the manual provided by the Brazilian Ministry of Health and are further described in Supplementary File 1. Brazil's territory was divided into five regions according to the official division of the country as established by the Brazilian Institute of Geography and Statistics. The dates of case occurrences were stratified by season. Variables with more than 10% missing data, such as race, educational levels, imaging test results, and use of antiviral medication were not included in the analysis. The proportion of missing data in the remaining variables is displayed in Supplementary File 1.

Statistical analysis

Median values with interquartile ranges (IQR) were used as measures of central tendency and dispersion, respectively. The Kolmogorov-Smirnov test was used to compare continuous variables. Categorical variables were presented as absolutes numbers and frequencies (%) and were compared using Fisher's exact test. The Bonferroni adjustment for multiple comparisons was employed. Binary regression analyses, backwards stepwise method, assessed the association between clinical features and the etiologic agent, considering potential confounders. All variables with statistical relevance ($p < 0.1$ in the univariable analysis) were included in the

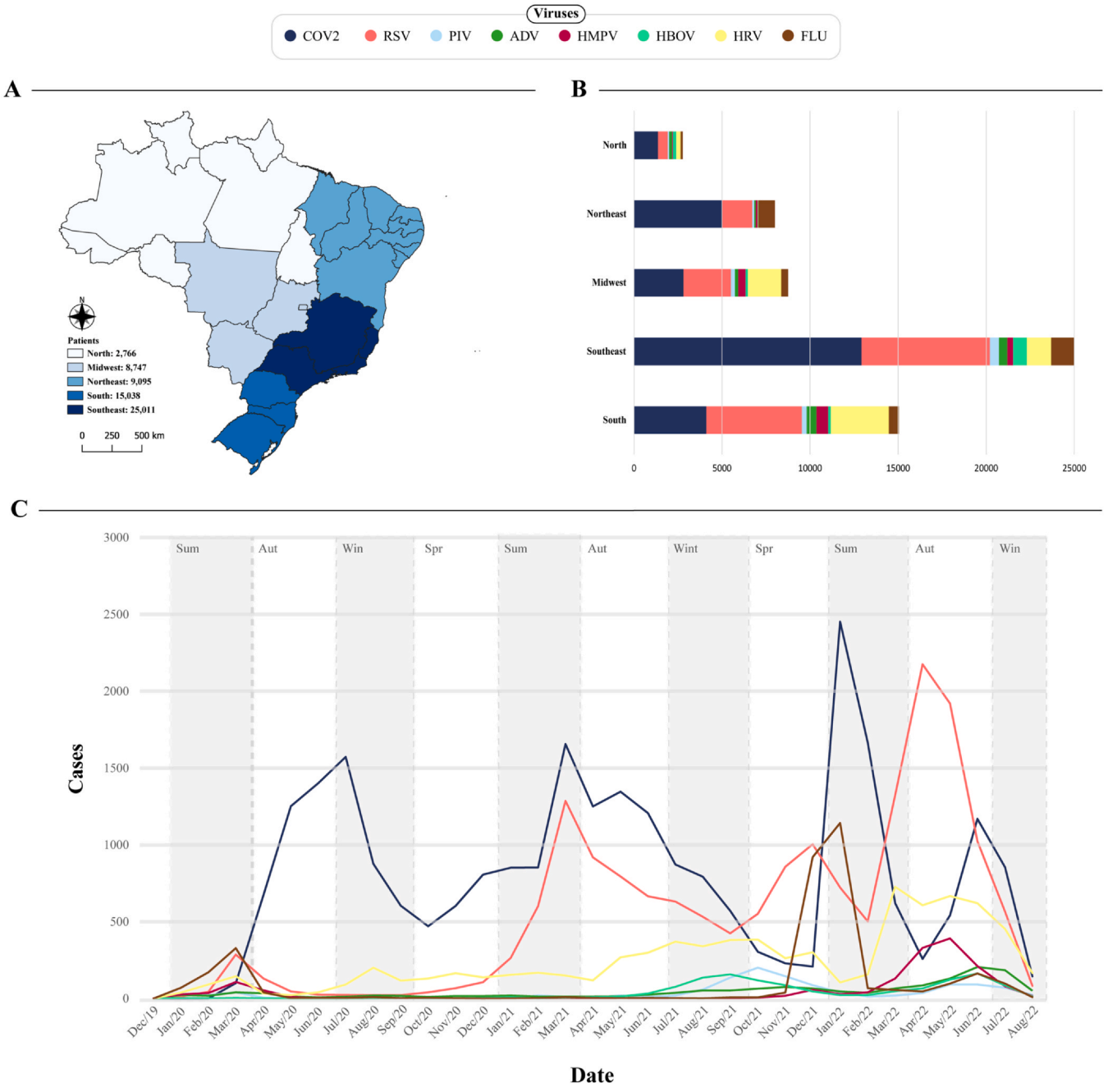

Fig. 2. Case notifications according to the Brazilian macro-region. (A) Choropleth map showing case density per macro-region of Brazil. (B) Bar chart representing viral prevalence per macro-region of Brazil. (C) Viral occurrences by date. Each line represents the viral incidence per month. Gray bars represent the seasons. Abbreviations: SARS-CoV-2 (COV2), Respiratory Syncytial Virus (RSV), Parainfluenza Virus (PIV), Human metapneumovirus (HMPV), Adenovirus (ADV), Human Bocavirus (HBOV), Human Rhinovirus (HRV), Influenza (FLU), Summer (Sum), Autumn (Aut), Winter (Win), Spring (Spr).

model. Differences with p-values below 0.05 were considered statistically significant. Statistical analyses were performed in SPSS (version 26.0.0.0) and R (version 4.1.1) with the packages compareGroups (version 4.5.1) and fmsb (0.7.3). The map was designed using qGIS (version 3.24.3).

Ethics statement

All data analyzed in this study were obtained from a public government program. They were pre-processed by the Brazilian Ministry of Health and published in https://opendatasus.saude.gov.br/. The datasets are verified for duplicate registration, consistency, and completeness of registered data, following the regulations dictated by Resolution No. 466/12 on Research Ethics of the National Health Council, Brazil.

Results

Patient enrollment and viral etiology

There were 296,752 entries in the national registry for individuals younger than 20 years between February 2020 and August 2022. Of these, 60,657 had a viral infection confirmed by RT-PCR. The main viral agents detected in the period were COV2 (43.2%), RSV (29.1%), HRV (13.1%) and FLU (5.5%). Most cases were younger than 5 years (55.1%; median age 1.56; IQR: 0.38–5.69), males (54.4%), from

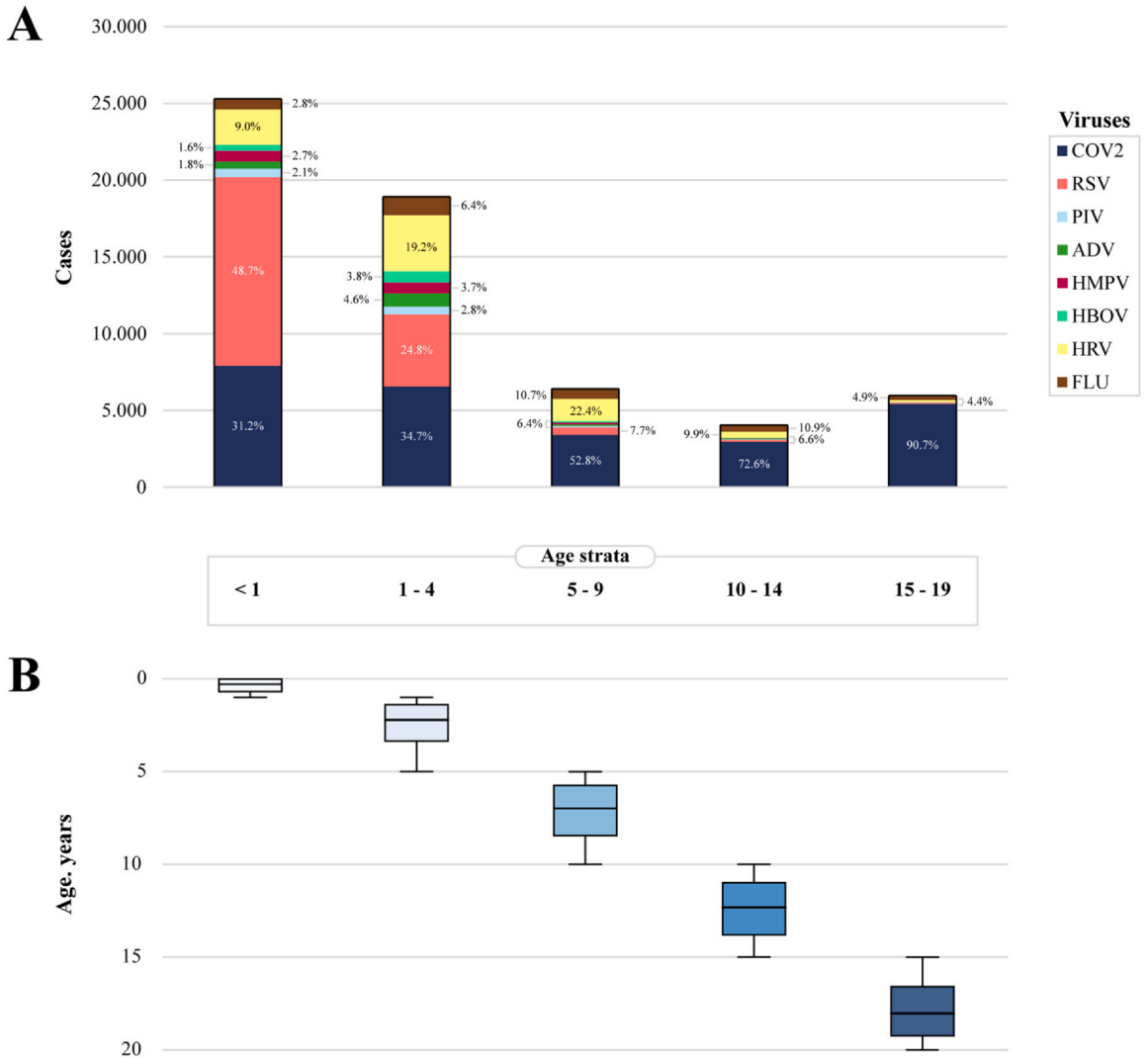

Fig. 3. Viral occurrences by age strata. (A) Each bar represents the absolute viral incidence by age. (B) Boxplot showing age distribution (median and interquartile range) in each stratum. Abbreviations: SARS-CoV-2 (COV2), Respiratory Syncytial Virus (RSV), Parainfluenza Virus (PIV), Human metapneumovirus (HMPV), Adenovirus (ADV), Human Bocavirus (HBOV), Human Rhinovirus (HRV), Influenza (FLU).

the southeastern region of Brazil (41.2%) and occurred in the autumn (36.4%). Regarding unfavorable clinical outcomes, 15,495 (25.6%) patients were admitted to the intensive care unit (ICU), 5397 (8.9%) required mechanical ventilation, and 2636 (4.3%) died. The sample composition was represented in Fig. 1.

Comparison of baseline characteristics

The distribution of severe respiratory virus infections varied by region (Fig. 2A and B). The southeast had the highest number of cases, COV2 (51%) and RSV (29%) were the most prevalent viruses. The north had similar proportions of COV2 (43%) and RSV (29%), but the smallest number of cases. The south had the second highest number of cases, with RSV (36%) being the most common, followed by COV2 (27%) and HRV (21%). In the Midwest, COV2 (32%), RSV (30%), and HRV (21%) were the most common viruses. The northeast had the highest proportion of COV2 cases (62%), followed by RSV (21%) and FLU (11%). Seasonally, there were more notifications in late summer and early autumn of the southern hemisphere, exceptionally PIV and FLU were more prevalent in spring and ADV and BOV were in winter (Figs. 2C and S1).

The population was categorized into five age groups to assess their proportion of viral involvement (Fig. 3). There were 25,293 cases of children under one year (median: 0.29 [IQR: 0.13 – 0.57]). In this group there was a major prevalence of RSV (48.7%), followed by COV2 (31.2%) and HRV (9.0%). The age group of 1–4 years (median: 2.22; IQR: 1.52–3.23) presented greater diversity of viral involvement. The main viruses reported were COV2 in 34.7%, RSV in 24.8% and HRV in 19.2%. Between 5 and 9 years (median: 5.87; IQR: 8.33–12.32) 6425 cases were observed. The COV2 was notified in 52.8%, HRV in 22.4% and FLU 10.7%. The smallest group consisted of cases aged 10–14 years (median: 12.3; IQR: 11.1–13.8). In this group, COV2 was more common (72.6%), followed by FLU (10.9%) and HRV (9.9%). Finally, in the age group of 15–20 years (median: 18.0; IQR: 16.7–19.1), COV2 corresponded for 90.7% of the cases, FLU for 4.9% and HRV for 3%. In summary, COV2 was predominant in al-most all age groups, except for the children under one year, for this group RSV was the most prevalent.

There were 11,631 (19.2%) children with at least one comorbidity. Asthma was the most prevalent comorbidity, and it was significantly higher in patients diagnosed with HRV (13.2%), FLU (8.8%) and COV2 (6.1%). Neuropathy and immunosuppression frequencies were higher in patients with COV2 and PIV. In addition, heart disease, obesity and diabetes were higher only in children with COV2. As this was not an exclusive database for evaluating children, data on

Table 1
Population characteristics.

Characteristics	General population [n = 60,657]	SARS2 [n = 26,212] (a)	RSV [n = 17,677] (b)	PIV [n = 1221] (c)	ADV [n = 1481] (d)	HMPV [n = 1561] (e)	HBOV [n = 1262] (f)	HRV [n = 7920] (g)	FLU [n = 3323] (h)	p-value
Season no. (%)										< 0.001
Summer	17,803 (29.4)	8200 (31.3) b c d e f g	5043 (28.5) c d e f g	202 (16.5) f	277 (18.7) f	373 (23.9) c d f	119 (9.4)	1739 (22.0) c f	1850 (55.7) a b c d e f g	
Autumn	22,052 (36.4)	9100 (34.7) c h	7701 (43.6) a c d f g h	265 (21.7) h	529 (35.7) c h	1002 (64.2) a b c d f g h	410 (32.5) c h	2679 (33.8) c h	366 (11.0)	
Winter	12,169 (20.1)	6289 (24.0) b e h	2304 (13.0) e h	319 (26.1) b e h	426 (28.8) a b e h	102 (6.5) h	474 (37.6) a b c d e g h	2121 (26.8) a b e h	134 (4.0)	
Spring	8633 (14.2)	2623 (10.0) e	2629 (14.9) a e	435 (35.6) a b d e f g h	249 (16.8) a e	84 (5.4)	259 (20.5) a b e	1381 (17.4) a b e	973 (29.3) a b d e f g	
Country region no. (%)										< 0.001
North	2766 (4.6)	1369 (5.2) b e g h	558 (3.2)	76 (6.2) b e g h	167 (11.3) a b c e g h	43 (2.8)	190 (15.1) a b c e g h	248 (3.1)	115 (3.5)	
Northeast	9095 (15)	4996 (19.1) b c d e f g	1719 (9.7) d f	125 (10.2) d f	79 (5.3) f	117 (7.5) f	17 (1.3)	1100 (13.9) b c d e f	942 (28.3) a b c d e f g	
Midwest	8747 (14.4)	2814 (10.7)	2695 (15.2) a f h	225 (18.4) a d f h	198 (13.4) a	410 (26.3) a b c d f h	133 (10.5)	1888 (23.8) a b c d f h	384 (11.6)	
Southeast	25,011 (41.2)	12,926 (49.3) b c d e g h	7278 (41.2) d e g	518 (42.4) d e g	480 (32.4) e g	325 (20.8)	778 (61.6) a b c d e g h	1389 (17.5)	1317 (39.6) d e g	
South	15,038 (24.8)	4107 (15.7) f	5427 (30.7) a c f h	277 (22.7) a f h	557 (37.6) a b c f h	666 (42.7) a b c f h	144 (11.4)	3295 (41.6) a b c f h	565 (17.0) f	
Male sex no. (%)	32,996 (54.4)	13,880 (53.0)	9737 (55.1) a e	664 (54.4)	823 (55.6)	787 (50.4)	718 (56.9) e	4565 (57.7) a b e	1822 (54.8)	< 0.001
Age no. (%)										< 0.001
[< 1]. years	25,293 (41.7)	7894 (30.1) h	12,312 (69.6) a c d e f g h	540 (44.2) a d f g h	463 (31.3) h	689 (44.1) a d f g h	409 (32.4) h	2291 (28.9) h	695 (20.9)	
[0–4]. years	18,910 (31.2)	6557 (25)	4681 (26.5) a	523 (42.8) a b h	868 (58.6) a b c e g h	706 (45.2) a b h	735 (58.2) a b c e g h	3630 (45.8) a b h	1210 (36.4) a b	
[5–9]. years	6425 (10.6)	3395 (13) b c d e f	497 (2.8).	95 (7.8) b	105 (7.1) b	116 (7.4) b	96 (7.6) b	1436 (18.1) a b c d e f	685 (20.6) a b c d e f	
[10–14]. years	4057 (6.7)	2947 (11.2) b c d e f g	136 (0.8).	46 (3.8) b f	31 (2.1) b	36 (2.3) b	19 (1.5)	400 (5.1) b d e f	442 (13.3) a b c d e f g	
[15–19]. years	5972 (9.8)	5419 (20.7) b c d e f g h	51 (0.3)	17 (1.4) b f	14 (0.9) b	14 (0.9) b	3 (0.2)	163 (2.1) b f	291 (8.8) b c d e f g	
Hospital acquired infection no. (%)	1347 (2.2)	829 (3.2) b d e g h	194 (1.1)	51 (4.2) b d e g h	16 (1.1)	16 (1.0)	30 (2.4) b	145 (1.8) b	66 (2.0) b	< 0.001
Symptoms no. (%)										
Fever	40,590 (66.9)	17,617 (67.2) b g	11,354 (64.2) g	856 (70.1) b g	1164 (78.6) a b c f g	1268 (81.2) a b c f g	845 (67.0) g	4699 (59.3)	2787 (83.9) a b c d f g	< 0.001
Cough	46,396 (76.5)	16,586 (63.3)	15,782 (89.3) a c d f g h	1015 (83.1) a	1225 (82.7) a	1385 (88.7) a c d g h	1074 (85.1) a	6553 (82.7) a	2776 (83.5) a	< 0.001
Sore throat	6580 (10.8)	3634 (13.9) b c e f g	989 (5.6)	88 (7.2)	183 (12.4) b c e	124 (7.9) b	113 (9.0) b	824 (10.4) b c	625 (18.8) a b c d e f g	< 0.001
Dyspnea	42,648 (70.3)	15,714 (59.9)	14,482 (81.9) a c d g h	855 (70) a	998 (67.4) a	1251 (80.1) a c d h	1007 (79.8) a c d h	6161 (77.8) a c d h	2180 (65.6) a	< 0.001
Desaturation	28,377 (46.8)	9982 (38.1)	9956 (56.3) a c d g h	545 (44.6) a h	701 (47.3) a h	942 (60.3) a c d g h	702 (55.6) a c d h	4252 (53.7) a c d h	1297 (39.0)	< 0.001
Diarrhea	6174 (10.2)	3338 (12.7) b c e g h	1403 (7.9)	88 (7.2)	211 (14.2) b c e g h	131 (8.4)	131 (10.4) g	572 (7.2)	300 (9.0) g	< 0.001
Vomiting	9382 (15.5)	4440 (16.9) b c g	2363 (13.4)	158 (12.9)	271 (18.3) b c g	229 (14.7)	183 (14.5)	1149 (14.5)	589 (17.7) b c g	< 0.001
Odynophagia	829 (1.4)	663 (2.5) b c d e f g h	73 (0.4)	4 (0.3)	8 (0.5)	7 (0.4)	2 (0.2)	42 (0.5)	30 (0.9) b	< 0.001
Ageusia	1006 (1.7)	765 (2.9) b c d e f g h	106 (0.6)	4 (0.3)	12 (0.8)	7 (0.4)	6 (0.5)	71 (0.9)	35 (1.1)	< 0.001
Abdominal pain	3073 (5.1)	1834 (7.0) b c e f g	425 (2.4)	34 (2.8)	73 (4.9) b	50 (3.2)	48 (3.8)	416 (5.3) b c e	193 (5.8) b c e	< 0.001
Myalgia	1051 (1.7)	883 (3.4) b c d e f g	24 (0.1)	5 (0.4)	7 (0.5)	3 (0.2)	1 (0.1)	49 (0.6) b	79 (2.4) b c d e f g	< 0.001
Arthralgia	49 (0.1)	42 (0.2) b g	1 (0.0)	0 (0.0)1	0 (0.0)1	0 (0.0)1	0 (0.0)1	1 (0.0)	5 (0.2) b g	< 0.001
Headache	1815 (3)	1488 (5.7) b c d e f g h	55 (0.3)	13 (1.1) b	15 (1.0) b	11 (0.7)	5 (0.4)	119 (1.5) b f	109 (3.3) b c d e f g	< 0.001
Comorbidities no. (%)										
Heart disease	1595 (2.6)	975 (3.7) b d g h	254 (1.4)	32 (2.6) b	31 (2.1)	44 (2.8) b	27 (2.1)	167 (2.1) b	65 (2.0)	< 0.001
Hematologic disease	607 (1)	409 (1.6) b g	52 (0.3)	16 (1.3) b	9 (0.6)	12 (0.8)	7 (0.6)	52 (0.7) b	50 (1.5) b g	< 0.001
Down syndrome	779 (1.3)	424 (1.6) b g h	169 (1.0)	16 (1.3)	25 (1.7) g	36 (2.3) b g h	17 (1.3)	62 (0.8)	30 (0.9)	< 0.001
Liver disease	204 (0.3)	116 (0.4) b	30 (0.2)	10 (0.8) b	6 (0.4)	2 (0.1)	5 (0.4)	23 (0.3)	12 (0.4)	< 0.001

(*continued on next page*)

Table 1 (*continued*)

Characteristics	General population [n = 60,657]	SARS2 [n = 26,212] (a)	RSV [n = 17,677] (b)	PIV [n = 1221] (c)	ADV [n = 1481] (d)	HMPV [n = 1561] (e)	HBOV [n = 1262] (f)	HRV [n = 7920] (g)	FLU [n = 3323] (h)	p-value
Asthma	3716 (6.1)	1602 (6.1) b c d e	544 (3.1)	41 (3.4)	60 (4.1)	61 (3.9)	73 (5.8) b	1042 (13.2) a b c d e f h	293 (8.8) a b c d e f	< 0.001
Diabetes	580 (1)	487 (1.9) b c d e f g h	23 (0.1)	3 (0.2)	3 (0.2)	3 (0.2)	4 (0.3)	28 (0.4) b	29 (0.9) b g	< 0.001
Neurologic disease	2377 (3.9)	1426 (5.4) b e f g	273 (1.5)	68 (5.6) b	53 (3.6) b	52 (3.3) b	41 (3.2) b	316 (4.0) b	148 (4.5) b	< 0.001
Lung disease	1071 (1.8)	520 (2.0) b	194 (1.1)	23 (1.9)	26 (1.8)	30 (1.9)	20 (1.6)	202 (2.6) b	56 (1.7)	< 0.001
Immunodepression	1347 (2.2)	878 (3.3) b d e f g h	150 (0.8)	43 (3.5) b d e f h	16 (1.1)	15 (1.0)	17 (1.3)	168 (2.1) b	60 (1.8) b	< 0.001
Kidney disease	521 (0.9)	350 (1.3) b d f g	50 (0.3)	13 (1.1) b	5 (0.3)	9 (0.6)	4 (0.3)	66 (0.8) b	24 (0.7) b	< 0.001
Obesity	758 (1.2)	683 (2.6) b c e f g h	31 (0.2)	3 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	33 (0.4) b	6 (0.2)	< 0.001
Cancer	300 (0.5)	174 (0.7) b	56 (0.3)	2 (0.2)	1 (0.1)	4 (0.3)	6 (0.5)	38 (0.5)	19 (0.6)	< 0.001
ICU admission no. (%)	15,495 (25.5)	7149 (27.3) b c d e g h	4571 (25.9) d e h	271 (22.2)	306 (20.7)	293 (18.8)	315 (25.0) e h	1926 (24.3) e h	664 (20.0)	< 0.001
Mechanical ventilation no. (%)	5397 (8.9)	2650 (10.1) b g h	1464 (8.3)	94 (7.7) g	135 (9.1)	130 (8.3)	111 (8.8)	555 (7.0)	258 (7.8)	< 0.001
Death no. (%)	2636 (4.3)	1987 (7.6) b c d e f g h	222 (1.3)	20 (1.6)	58 (3.9) b c g	45 (2.9) b	33 (2.6) b	148 (1.9) b	123 (3.7) b c g	< 0.001

Table note: Results are based on bilateral tests. A letter was consecutively assigned for each viral agent. For each pair of columns, the column proportions are compared, and Bonferroni adjustments are used to adjust the significance values. For each significant pair, the letter of the smaller category is placed under the column with the larger proportion (e.g., if the latter b appears under the column a, it means that the columns a has a significant higher proportion than b for that specific comparison. Significance level for lowercase letters (a, b, c): $p < 0.05$.

prematurity were absent. It is important to notice that 2.2% of the cases were acquired in a health care unit, and COV2 and PIV stood out as the main etiological agents in these cases. Detailed characteristics of the study subjects are shown in Table 1.

Comparison of Signs and symptoms

The most common signs or symptoms reported were cough (76.5%), respiratory discomfort (70.3%), fever (66.9%) and desaturation (46.8%). To evaluate the potential bias of communication ability, the age of 5 years was used as a cutoff point. In general, the distribution pattern of clinical manifestations was similar when classified for etiologic agents and the patient's age group (Table S1 and Fig. S2). As expected, ageusia, anosmia, headache, arthralgia, or myalgia were fewer than 1% for any virus among children under 5 years of age. For those over 5 years old, the percentage of arthralgia cases remained less than 1% for all viruses (Table S2).

After adjusting for country region, seasonality, comorbidities, and age, significant differences were found in the clinical presentation of viral infections. COV2 was associated with the less likelihood to present cough (aOR: 0.34; 95%CI: 0.32–0.36), respiratory discomfort (aOR: 0.61; 95%CI: 0.59–0.64) and desaturation (OR: 0.71; 95%CI: 0.69–0.75) when compared to other viruses. Also, it was the only virus to present a positive association with anosmia (aOR: 1.40; 95%CI: 1.14–1.73), ageusia (aOR: 1.74; 95%CI: 1.37–2.19), headache (aOR: 1.60; 95%CI: 1.39–1.85), myalgia (aOR: 1.80; 95%CI: 1.48–2.19) and abdominal pain (aOR: 1.13; 95%CI: 1.03–1.23). The presence of diarrhea was associated with cases of COV2 (aOR: 1.14; 95%CI 1.10–1.19) and ADV (aOR1.34; 95%CI 1.15–1.56). Sore throat stood out positively only among FLU cases (aOR: 1.48; 95%CI: 1.34–1.64). Similarly, respiratory discomfort and desaturation were positively associated with RSV, HMPV, HBOV and HRV. The presence of fever was negatively associated in RSV (aOR 0.89; 95%CI 0.85–0.93) and HRV (aOR 0.58; 95%CI 0.55–0.61) cases. Vomiting was not associated with any viral manifestation (Figs. 4 and S3).

Discussion

In this retrospective cohort study, severe lower respiratory virus infections in pediatric patients during the COVID-19 pandemic were characterized by comparing the age of occurrence, seasonal profile, and clinical presentation of eight viral species from laboratory-confirmed cases in the Brazilian National Influenza Surveillance Epidemiological System from February 2020 to August 2022. To the best of current understanding, this is the largest study on this issue to date.

Viral pathogens play a significant role in the incidence of LRTIs, and technological advances have improved our understanding about them and their identification on common respiratory illnesses, as well as, during outbreak scenarios [14,15]. Thus, in the early 2000 s, it was possible to identify new viruses related to LRTI, such as human metapneumovirus and bocavirus. Studies have been conducted to establish their clinical relevance and severity [16–18]. Respiratory syncytial virus and human rhinovirus were identified as the most prevalent viral agents of LRTI, present in 22.7% and 22.1% of cases respectively, by a meta-analysis of laboratory-confirmed viral infections, from 1995 to 2019, in 152,000 children younger than 19 years old with community-acquired pneumonia [19]. Similarly, a multicentric Brazilian study that evaluated 507 children under 24 months with LRTI also found a higher prevalence of RSV (40.2%) and HRV (17%) between 2012 and 2013 [20]. Influenza and coronaviruses, while less common causes of pneumonia in these studies, can cause severe respiratory disease and outbreaks, as previously seen in the SARS-CoV-1 pandemic in 2003 and the H1N1 influenza pandemic in 2009 [19]. Brazilian national data corroborate that the influenza virus was the main agent related to severe respiratory disease in 2019, among all age strata [21]. Whereas it is worth noting that in Brazil, before the COVID-19 pandemic, the use of viral panels was often restricted, so in this period studies on this subject were limited.

Brazil is currently the third most affected country in COVID-19 pandemic, with 36 million confirmed cases and 695,000 related deaths until December 2022 [22]. Our study demonstrates that, between 2020

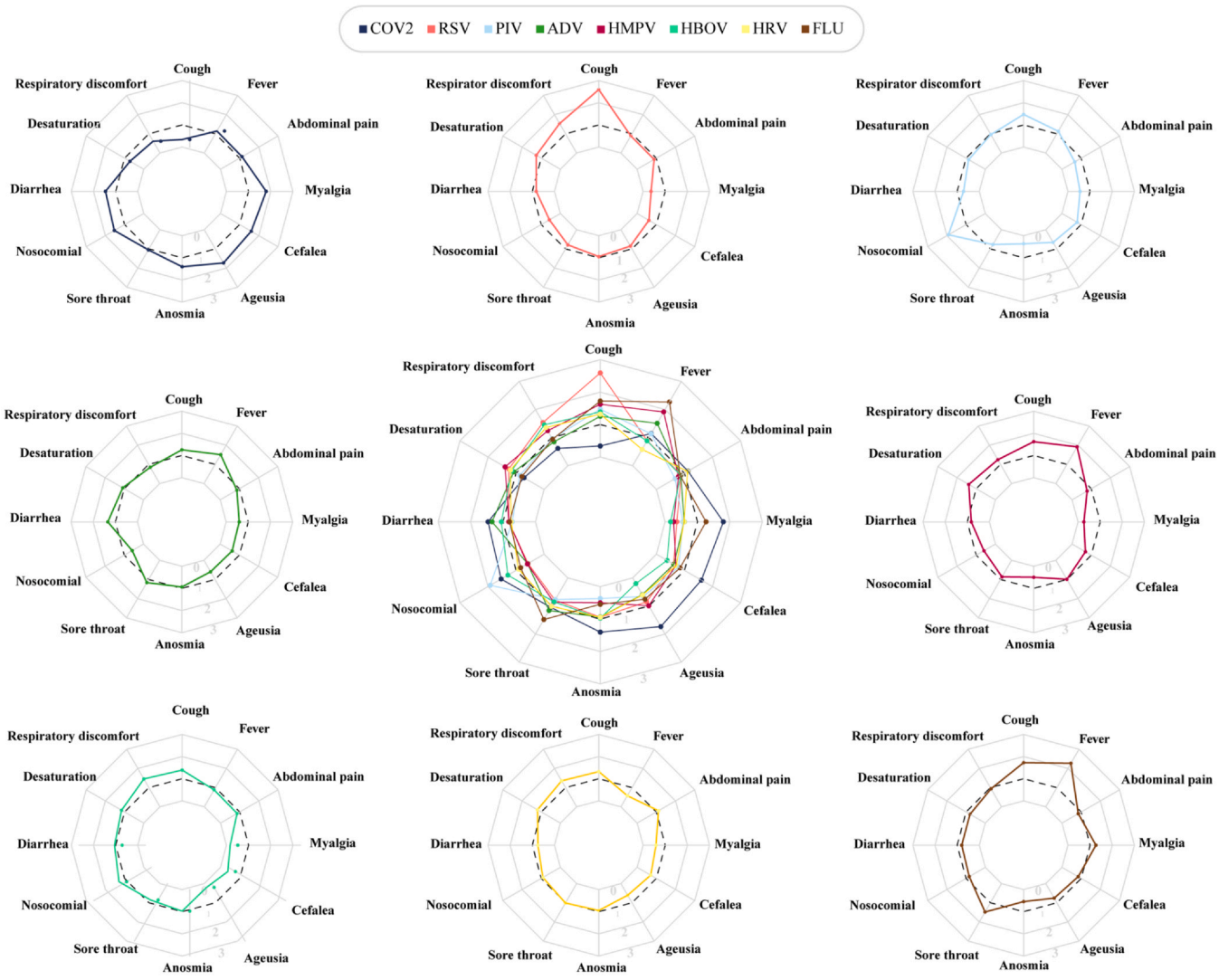

Fig. 4. Viral symptom profile. Each axis represents the adjusted odds ratio of a virus being associated with a symptom. The dotted line represents nullity, or an odd of 1. Points below this line suggest they refer to an inverse association. Abbreviations: SARS-CoV-2 (COV2), Respiratory Syncytial Virus (RSV), Parainfluenza Virus (PIV), Human metapneumovirus (HMPV), Adenovirus (ADV), Human Bocavirus (HBOV), Human Rhinovirus (HRV), Influenza (FLU).

and 2022, COV2 was the most detected virus in children (43.2%), except for those younger than 1 year old. For this group, RSV remained the major cause of respiratory tract infections, which emphasizes the importance of this pathogen in this age group, already evidenced in previous studies [23]. We found that children between the ages of 1–4 had a greater diversity of viruses causing respiratory tract infections, which is expected, given the increased social exposure of this age group, including increased contact with other children in day care centers and leisure areas, as well as immunological immaturity [24]. We also observed that COV2 infection was predominant in adolescents in the pre-vaccine period, with a significant drop in cases as vaccination for this population progressed.

The first cases of COV2 in Brazil were reported in February 2020. Its first wave was preceded by smaller outbreaks of other respiratory viruses, such as FLU, RSV, HRV and HMPV. During the first 9 months of the pandemic, most severe cases were caused by COVID-19. Importantly, this period coincided with the autumn and winter months in the southern hemisphere when viral respiratory infections such as RSV-related disease are typically expected. Authors from United States, Canada, China, Australia and Belgium also reported a decrease in normal seasonal illness attributable to other respiratory viruses in children during these early months of the pandemic, which may be attributed to the implementation of protective measures to control the spread of COVID-19, as well as, changes in healthcare seeking behavior [25–28].

The second wave of COV2 started in November 2020 and ended in December 2021. It is important to note that vaccination against COVID-19 in Brazil started in January 2021, initially prioritizing very elderly patients and those with comorbidities that may lead to worse outcomes from COVID-19. Only in August 2021 the national vaccination for children under 20 without comorbidities commenced. Simultaneously, during this second wave of COV2, there was also an increase in cases of RSV from January 2021 to September 2021, outside of this virus' typical seasonality. This characterized a delayed RSV peak also described in other countries [23,28]. In the spring, there was a decline in COV2 cases, but an increase in notifications of RSV, HRV, PIV, and HBOV, followed by an increase in cases of influenza. One of the reasons for this growth was the low national FLU vaccine coverage, which reached 72.1% of the target audience in 2021 [29].

The third wave of COVID-19 occurred from December 2021 to April 2022. During the summer, FLU also represented an important proportion of new LRTI cases. In the autumn, there was an increase in cases of RSV, HRV, and HMPV. In our study, the last wave of COV2 began in August 2022. Overall, we demonstrated that the epidemiology of respiratory

viruses has been substantially impacted by the COVID-19 pandemic. Of note, during the years 2021 and 2022, few studies have been published on the burden of severe LRTI cases caused by other respiratory viruses and how they have been affected by the COVID-19 pandemic.

By considering seasonal, environmental, and clinical factors, this study was able to trace the profiles of the different viral agents that cause severe LRTI. Similarly to what we have found about clinical manifestations, a Vietnamese study with 4885 patients of all age groups found that patients with influenza were more likely to present fever, sore throat, and myalgia, while those with coronavirus infection presented myalgia [30]. Rudge et al. also reported the association of rhinovirus with headache, which was not corroborated in our study. Likewise, other previous studies could not accurately identify characteristics related to specific viral agents [31,32].

The presence of desaturation or respiratory distress in previous studies showed great variability. In children, studies involving pre-pandemic coronavirus strains showed that 59–69% had respiratory distress, while for SARS-COV-2 this rate was 21% [33–35]. Regarding RSV, HMPV, HBOV and HRV, the presence of desaturation ranged from 14% to 82%, 4–62%, 25–52% and 11–51% [17,32,36–38]. For respiratory distress it ranged 70–98%, 62–69%, 65–100% and 61–79% respectively [34,35,38]. Diarrhea is a rarely reported symptom with the highest prevalence in ADV infections (29%) [39]. Sore throat was reported in 38% of children with influenza in the study by Taylor et al. [40]. At last, previous studies have demonstrated a prevalence of fever ranging from 42% to 95% and 36–88% during RSV and HRV infections in children [34,38].

This study has several limitations. First, as it only analyzed children with severe LRTI, the validity of the described associations in other subpopulations is limited. Furthermore, this was an epidemiological surveillance record that covers all age groups; hence, more specific types of data, such as prematurity, were not available. Also, the database had a high rate of missing values, such as ethnicity and education. Nevertheless, the country regions where the patient lives, which were reported in the article, might serve as a proxy for inequality. Finally, no information on the specific criteria for RT-PCR testing was available. Regardless of such limitations, this is a study based on a large national registry with laboratory confirmation by molecular test, the notification of which is mandatory.

Conclusions

Our study provides valuable insights into severe lower respiratory virus infections in pediatric patients. The results highlight the varying degrees of association between viral agents and clinical and epidemiological characteristics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.09.015.

References

[1] Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. JAMA 1974;227:164–9.

[2] Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1204–22. https://doi.org/10.1016/S0140-6736(20)30925-9

[3] Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta-analysis. J Glob Health 2015;5:010408. https://doi.org/10.7189/jogh.05.010408

[4] Jartti T, Söderlund-Venermo M, Hedman K, Ruuskanen O, Mäkelä MJ. New molecular virus detection methods and their clinical value in lower respiratory tract infections in children. Paediatr Respir Rev 2013;14:38. https://doi.org/10.1016/j.prrv.2012.04.002

[5] Popp M, Stegemann M, Riemer M, Metzendorf M-I, Romero CS, Mikolajewska A, et al. Antibiotics for the treatment of COVID-19. Cochrane Database Syst Rev 2021;10:CD015025. https://doi.org/10.1002/14651858.CD015025

[6] Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database Syst Rev 2014;2014:CD008965. https://doi.org/10.1002/14651858.CD008965.pub4

[7] Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev 2020;11:CD006207. https://doi.org/10.1002/14651858.CD006207.pub5

[8] Secretaria de Vigilância em Saúde. Vigilância em Saúde no Brasil 2003|2019, 2019.

[9] Kyu HH, Vongpradith A, Sirota SB, Novotney A, Troeger CE, Doxey MC, et al. Age–sex differences in the global burden of lower respiratory infections and risk factors, 1990–2019: results from the Global Burden of Disease Study 2019. Lancet Infect Dis 2022;22:1626–47. https://doi.org/10.1016/S1473-3099(22)00510-2

[10] Arruda E, Jones MH, Escremim De Paula F, Chong D, Bugarin G, Notario G, et al. The Burden of Single Virus and Viral Coinfections on Severe Lower Respiratory Tract Infections Among Preterm Infants: A Prospective Birth Cohort Study in Brazil. Pedia Infect Dis J 2014;33:997–1003. https://doi.org/10.1097/INF.0000000000000349

[11] Prietsch SOM, Fischer GB, César JA, Lempek BS, Barbosa Jr. LV, Zogbi L, et al. Acute lower respiratory illness in under-five children in Rio Grande, Rio Grande do Sul State, Brazil: prevalence and risk factors. Cad Saúde Pública 2008;24:1429–38. https://doi.org/10.1590/S0102-311×2008000600023

[12] Corrêa RDA, José BPDS, Malta DC, Passos VMDA, França EB, Teixeira RA, et al. Carga de doença por infecções do trato respiratório inferior no Brasil, 1990 a 2015: estimativas do estudo Global Burden of Disease 2015. Rev Bras Epidemiol 2017;20:171–81. https://doi.org/10.1590/1980-5497201700050014

[13] Secretaria de Vigilância em Saúde do Ministério da Saúde. Guia de Vigilância Epidemiológica Covid-19: Emergência de Saúde Pública de Importância Nacional pela Doença pelo Coronavírus 2019. n.d.

[14] Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet 2011;377:1264–75. https://doi.org/10.1016/S0140-6736(10)61459-6

[15] Ren L, Xiang Z, Guo L, Wang J. Viral Infections of the Lower Respiratory Tract. Curr Infect Dis Rep 2012;14:284–91. https://doi.org/10.1007/s11908-012-0258-4

[16] Wang X, Li Y, Deloria-Knoll M, Madhi SA, Cohen C, Ali A, et al. Global burden of acute lower respiratory infection associated with human metapneumovirus in children under 5 years in 2018: a systematic review and modelling study. Lancet Glob Health 2021;9:e33–43. https://doi.org/10.1016/S2214-109X(20)30393-4

[17] García-García ML, Calvo C, Rey C, Díaz B, Molinero M del M, Pozo F, et al. Human metapnuemovirus infections in hospitalized children and comparison with other respiratory viruses. 2005-2014 prospective study. PLOS ONE 2017;12:e0173504. https://doi.org/10.1371/journal.pone.0173504

[18] Petrarca L, Nenna R, Frassanito A, Pierangeli A, Di Mattia G, Scagnolari C, et al. Human bocavirus in children hospitalized for acute respiratory tract infection in Rome. World J Pedia 2020;16:293–8. https://doi.org/10.1007/s12519-019-00324-5

[19] Pratt MTG, Abdalla T, Richmond PC, Moore HC, Snelling TL, Blyth CC, et al. Prevalence of respiratory viruses in community-acquired pneumonia in children: a systematic review and meta-analysis. Lancet Child Adolesc Health 2022;6:555–70. https://doi.org/10.1016/S2352-4642(22)00092-X

[20] Gurgel RQ, Bezerra PG, de M, Duarte M do CMB, Moura AÁ, Souza EL, Silva LS da S, et al. Relative frequency, Possible Risk Factors, Viral Codetection Rates, and Seasonality of Respiratory Syncytial Virus Among Children With Lower Respiratory Tract Infection in Northeastern Brazil. Med (Baltim) 2016;95:e3090. https://doi.org/10.1097/MD.0000000000003090

[21] Ministério da Saúde do Brasil. Informe Epidemiológico: Influenza. n.d.

[22] World Health Organization. Brazil: WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data. WHO Coronavirus COVID-19 Dashboard n.d. ⟨https://covid19.who.int⟩ (accessed December 17, 2022).

[23] Saravanos GL, Hu N, Homaira N, Muscatello DJ, Jaffe A, Bartlett AW, et al. RSV Epidemiology in Australia Before and During COVID-19. Pediatrics 2022;149:e2021053537. https://doi.org/10.1542/peds.2021-053537

[24] Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc R Soc B Biol Sci 2015;282:20143085. https://doi.org/10.1098/rspb.2014.3085

[25] Haddadin Z, Schuster JE, Spieker AJ, Rahman H, Blozinski A, Stewart L, et al. Acute Respiratory Illnesses in Children in the SARS-CoV-2 Pandemic: Prospective Multicenter Study. Pediatrics 2021;148:e2021051462. https://doi.org/10.1542/peds.2021-051462

[26] Liu P, Xu M, Cao L, Su L, Lu L, Dong N, et al. Impact of COVID-19 pandemic on the prevalence of respiratory viruses in children with lower respiratory tract infections in China. Virol J 2021;18:159. https://doi.org/10.1186/s12985-021-01627-8

[27] Britton PN, Hu N, Saravanos G, Shrapnel J, Davis J, Snelling T, et al. COVID-19 public health measures and respiratory syncytial virus. Lancet Child Adolesc Health 2020;4:e42–3. https://doi.org/10.1016/S2352-4642(20)30307-2

[28] Shen DP, Vermeulen F, Debeer A, Lagrou K, Smits A. Impact of COVID-19 on viral respiratory infection epidemiology in young children: A single-center analysis.

Front Public Health 2022;10:931242. https://doi.org/10.3389/fpubh.2022.931242
[29] Ministério da Saúde do Brasil. Dashboard: Campanha Nacional de Vacinação contra a Influenza 2022 n.d. ⟨https://infoms.saude.gov.br/extensions/Influenza_2021/Influenza_2021.html⟩ (accessed January 8, 2023).
[30] Rudge JW, Inthalaphone N, Pavlicek R, Paboriboune P, Flaissier B, Monidarin C, et al. "Epidemiology and aetiology of influenza-like illness among households in metropolitan Vientiane, Lao PDR": A prospective, community-based cohort study. PLOS ONE 2019;14:e0214207. https://doi.org/10.1371/journal.pone.0214207
[31] Gooskens J, van der Ploeg V, Sukhai RN, Vossen AC, Claas EC, Kroes AC. Clinical evaluation of viral acute respiratory tract infections in children presenting to the emergency department of a tertiary referral hospital in the Netherlands. BMC Pedia 2014;14:297. https://doi.org/10.1186/s12887-014-0297-0
[32] Pierangeli A, Scagnolari C, Selvaggi C, Monteleone K, Verzaro S, Nenna R, et al. Virological and clinical characterization of respiratory infections in children attending an emergency department during the first autumn–winter circulation of pandemic A (H1N1) 2009 influenza virus. Clin Microbiol Infect 2012;18:366–73. https://doi.org/10.1111/j.1469-0691.2011.03590.x
[33] Bhalala US, Gist KM, Tripathi S, Boman K, Kumar VK, Retford L, et al. Characterization and Outcomes of Hospitalized Children With Coronavirus Disease 2019: A Report From a Multicenter, Viral Infection and Respiratory Illness Universal Study (Coronavirus Disease 2019) Registry. Crit Care Med 2022;50:e40–51. https://doi.org/10.1097/CCM.0000000000005232
[34] Nascimento-Carvalho AC, Vilas-Boas A-L, Fontoura M-SH, Vuorinen T, Nascimento-Carvalho CM. Respiratory viruses among children with non-severe community-acquired pneumonia: A prospective cohort study. J Clin Virol 2018;105:77–83. https://doi.org/10.1016/j.jcv.2018.06.003
[35] Góes LGB, Zerbinati RM, Tateno AF, Souza AV, Ebach F, Corman VM, et al. Typical epidemiology of respiratory virus infections in a Brazilian slum. J Med Virol 2020;92:1316–21. https://doi.org/10.1002/jmv.25636
[36] Furuse Y, Tamaki R, Suzuki A, Kamigaki T, Okamoto M, Saito-Obata M, et al. Epidemiological and clinical characteristics of children with acute respiratory viral infections in the Philippines: a prospective cohort study. e9-1037.e14 Clin Microbiol Infect 2021;27:1037. https://doi.org/10.1016/j.cmi.2020.09.017
[37] Laurent C, Dugué AE, Brouard J, Nimal D, Dina J, Parienti J-J, et al. Viral Epidemiology and Severity of Respiratory Infections in Infants in 2009: A Prospective Study. Pedia Infect Dis J 2012;31:827–31. https://doi.org/10.1097/INF.0b013e3182566005
[38] Kamata K, Thein KN, Di Ja L, Win NC, Win SMK, Suzuki Y, et al. Clinical manifestations and outcome of viral acute lower respiratory infection in hospitalised children in Myanmar. BMC Infect Dis 2022;22:350. https://doi.org/10.1186/s12879-022-07342-1
[39] Probst V, Spieker AJ, Stopczynski T, Stewart LS, Haddadin Z, Selvarangan R, et al. Clinical presentation and severity of adenovirus detection alone vs adenovirus co-detection with other respiratory viruses in US children with acute respiratory illness from 2016 to 2018. J Pedia Infect Dis Soc 2022;11:430–9. https://doi.org/10.1093/jpids/piac066
[40] Taylor S, Lopez P, Weckx L, Borja-Tabora C, Ulloa-Gutierrez R, Lazcano-Ponce E, et al. Respiratory viruses and influenza-like illness: Epidemiology and outcomes in children aged 6 months to 10 years in a multi-country population sample. J Infect 2017;74:29–41. https://doi.org/10.1016/j.jinf.2016.09.003