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Research Article

Prevalence of Influenza Associated with COVID-19 in Children

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ABSTRACT

Acute respiratory infections can be triggered by different pathogens, including Myxovirus influenzae. All age groups can be affected by this disease, but some are more susceptible to developing complications, such as children, who can develop Severe Acute Respiratory Syndrome (SARS). Therefore, the objective of this study were to investigate the prevalence of the influenza virus and its subtypes, with COVID-19 during the pandemic period and compare it with official case data. Samples were collected from pediatric patients suspected of having a respiratory virus infection between May 2020 and April 2022 in five hospitals, totaling 606 participants, and 59 participants were selected for the study because they had an infection caused by influenza. Together, a static analysis of the Secretary of State's SARS cases was carried out and compared with the study. Data from the secretariat indicate a reduction in Covid-19, starting from week 35. For influenza, the forecast follows the seasonality of 175 epidemiological weeks, with week 32 being the one with the highest predicted quantity. The children participating in the study present numbers proportionally similar to data from the epidemiological weeks, with mortality rate of 3.38%. The data obtained present proportionally similar numbers. Influenza is one of the main etiological agents causing acute respiratory infections in children, but strategies such as vaccination, rational use of antivirals and antibiotics minimize these infections.

Keywords: SARS; COVID-19; Surveillance; Epidemiology; Respiratory viruses

INTRODUCTION

Influenza is an acute respiratory infection, caused by the Myxovirus Influenzae virus belonging to the taxonomic family Orthomyxoviridae. It is a disease with high transmission and worldwide distribution. Its transmission occurs primarily through respiratory droplets produced during coughing, sneezing or talking from an otherwise susceptible infected person. Factors that promote its easy spread in epidemics, which can also cause pandemics [1,2].

Influenza infection presents different characteristics and symptoms in each individual, the most common symptoms are: Sudden onset of high fever, inflammation of the respiratory tract, headache, runny nose and cough. These manifestations occur around seven to 10 days [3].

Although the course of Influenza usually resolves spontaneously, some cases, especially in children, can progress to more serious conditions, such as Severe Acute Respiratory Syndrome (SARS). According to the protocol, SARS is described as a flu-like syndrome in any individual who presents dyspnea or one of the following signs: SpO_2 saturation < or =94% in the environment, discomfort from infections or increased respiratory rate, worsening of clinical conditions underlying disease, hypotension or acute respiratory failure during the seasonal period. Furthermore, for diagnostic purposes in children, limitations of nasal alae, cyanosis, intercostal insufficiency, dehydration and in appetence must be taken into account [4].

During the COVID-19 pandemic, there was great difficulty in determining the diagnosis of Influenza. We have already seen the occurrence of continuous co-circulation between the SARS-

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CoV-2 virus and the Influenza virus. Infection with these two viruses generates similar symptoms, and can occur alone or simultaneously, compromising treatment [5].

Therefore, the objectives of this study were to investigate the prevalence of the Influenza virus and its subtypes, with COVID-19 in children with SARS, during the pandemic period and to compare it to official data from the Health Department of the State of Goiás, Brazil (BR).`

MATERIALS AND METHODS

Ethical aspects

All sample collection and processing procedures and protocols were submitted and approved, under registration 33540320.7.0000.5078, by the Research Ethics Committee of the Hospital das Clínicas of the Federal University of Goiás, located in Goiânia-Goiás, Brazil. All parents of sick patients and volunteer donors signed the informed consent form.

Target population

This study included 606 patients with suspected respiratory virus infection, and 59 patients with Influenza infection, were selected for the study. The samples were collected in five hospitals in a capital in the Central-West region of Brazil. From May 2020 to April 2022. The following eligibility criteria were considered: Patients admitted to emergencies, Intensive Care Units (ICU), admissions to pediatric wards and hospital wards participating in the project.

Sample collection and processing

Nasal swab samples were collected for molecular analysis by RT-qPCR, in order to evaluate the presence of Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Influenza A, Influenza A (H1N1), Influenza B and SARS-COV2. All collected samples were kept at 4°C and sent to the Institute of Tropical Pathology and Public Health at the Federal University of Goiás, Goiás, Brazil. After processing, all samples were stored at -20°C. Samples were collected with a nasal swab and stored in MTV medium.

The genetic material (RNA) was extracted: Using Cellco kit® 2. Afterwards, reverse transcription was applied to obtain Complementary DNA (cDNA), using the IBMP® reverse transcriptase. The qPCR reaction was performed using the Termo Fisher® TaqMan Real-time Polymerase Chain Reaction master mix. The detection of amplification of genetic material was carried out using Applied One Step Real Time equipment.

The reverse transcription cycle followed by the PCR phase, consisted of a three to 10 seconds and denaturation step at 95°C. The DNA strands separated into single strands, followed by a hybridization step. After 15-45 seconds of polymerization at 55°C-60°C, for amplification of the primers and detection of the probes. In this step it was possible to hybridize with the single-stranded DNA templates and allow the polymerase to replicate the template, creating double-stranded DNA. This process was repeated 40 cycles. Samples were considered positive when the cycle threshold was between eight and 35.

Data from the Goiás (BR) health department and static analysis

SARS data from the Secretary of the State of Goiás (Brazil), were selected and analyzed, from the period between January 2020 and May 2023, corresponding to a total of 175 epidemiological weeks [6]. The statistical analysis of these data was carried out with the aid of Minitab® software version 19. For the analysis of seasonality and forecasting, a time series was considered with decomposition and forecast for the next 52 epidemiological weeks. Analyzes related to seasonality were considered for SARS by different etiological agents, considering COVID-19, Influenza virus and other respiratory viruses. The analysis was also carried out considering the general regardless of the etiological agent. A significance limit of 5% was considered for all statistical analyses.

RESULTS AND DISCUSSION

Based on data from the Department of Health of the State of Goiás (BR) described in Table 1, it is possible to observe the quantities of SARS by year, age group and etiological agent (Table1).

Table 1: Number of SARS cases per year and age group considering the etiological agents.

Year	Age group	SARS investigation	Unspecified SARS	SARS by COVID-19	Influenza SARS	SARS by another etiological agent	SARS by another respiratory virus	Total
2020	<2 years	0	541	112	5	1	144	803
2020	2 to 4 years	0	251	43	3	1	80	378
2020	5 to 9 years	3	236	52	1	4	45	341
2020	10 to 19 years	0	335	107	3	4	16	465
2020	20 to 29 years	3	677	726	7	10	13	1,436
2020	30 to 39 years	3	892	1,987	15	19	13	2,929
2020	40 to 49 years	6	1,106	3,237	7	15	16	4,387
2020	50 to 59 years	4	1,403	4,185	12	7	14	5,625
2020	>60 years	11	5,092	12,559	12	43	29	17,746
2021	<2 years	6	660	183	13	4	439	1,305

2021	2 to 4 years	6	341	98	11	0	167	623
2021	5 to 9 years	1	273	69	16	1	95	455
2021	10 to 19 years	2	314	390	12	2	18	738
2021	20 to 29 years	5	540	2,512	24	7	7	3,095
2021	30 to 39 years	10	704	7,010	6	12	10	7,752
2021	40 to 49 years	8	956	10,165	19	8	6	11,162
2021	50 to 59 years	13	1,205	11,812	20	8	9	13,067
2021	>60 years	16	4,338	21,661	124	42	33	26,214
2022	<2 years	6	923	342	58	6	707	2,042
2022	2 to 4 years	6	547	161	37	9	238	998
2022	5 to 9 years	1	416	128	46	1	128	720
2022	10 to 19 years	3	208	156	40	4	25	436
2022	20 to 29 years	5	192	318	21	4	8	548
2022	30 to 39 years	2	229	448	23	3	17	722
2022	40 to 49 years	4	307	623	26	4	11	975
2022	50 to 59 years	1	445	979	31	6	15	1,477
2022	>60 years	17	2,013	5,400	147	44	70	7,691
2023	<2 years	160	348	95	56	0	588	1,247
2023	2 to 4 years	34	198	55	33	0	94	414
2023	5 to 9 years	39	213	54	36	0	47	389
2023	10 to 19 years	19	70	21	26	0	11	147
2023	20 to 29 years	9	47	23	9	0	4	92
2023	30 to 39 years	13	49	40	19	0	2	123
2023	40 to 49 years	15	43	39	28	0	0	125
2023	50 to 59 years	24	57	67	11	0	5	164
2023	>60 years	72	272	400	46	0	19	809

During the period analyzed, the sample size was 117,640 participants, 54.6% male and 45.4% female. In 2020 and 2021, there were 23,008 and 53,900 cases of SARS due to Covid-19, respectively, and 65 and 245 cases of Influenza were reported. Until the 21st epidemiological week of 2020, 94,807 cases of hospitalization due to SARS were identified in Brazil, 31,968 cases due to COVID-19 and 1,463 due to Influenza [7].

Silva and collaborators during the analysis of the pandemic period from January to June 2020, in Pernambuco, Northeast of Brazil, determined that 66% of the SARS cases analyzed were due to COVID-19, followed by 2.5% of SARS cases due to Influenza and other respiratory diseases and 31.2% of SARS episodes had no specified cause [8].

Males were the most prevalent in reported cases, in addition, acute respiratory syndrome increased with increasing age, considering COVID-19, with 2021 standing out with 21,661 cases in the population aged >60 years. In relation to Influenza, this same age group presented 147 notifications in 2022.

In Brazil, between February 21, 2020 and September 21, 2020, 120,469 cases of hospitalization for SARS due to COVID-19 were recorded. Of these, 58.6% were men and 77.5% were aged 50 or over [9]. Data from the State of Rio Grande do Sul (BR) reported in SIVEP between January 2020 and October 3, 2020, correspond to the situation presented. 18,172 cases of SARS were confirmed, of which 54.46% were male. And the average age was 62 years old [10]. In contrast to these data, the female sex was predominant in the study developed by Binhardi, et al., for SARS cases due to Influenza A, corresponding to 54% of the samples. However, for Influenza B, males prevailed in 61.5% of reported cases [11].

Table 2 shows the main comorbidities of the epidemiological weeks analyzed. Cardiovascular diseases and diabetes were the most prevalent, demonstrating similarity with data published by other authors [12-14] (Table 2).

Table 2: Number of SARS cases per year and comorbidities considering the etiological agents.

Year	Comorbidities	SARS investigation	Unspecified SARS	SARS by COVID-19	Influenza SARS	SARS by another etiological agent	SARS by another respiratory virus	Total
2020	Down Syndrome	0	28	48	1	0	4	81
2020	Postpartum	0	56	43	0	1	1	101
2020	Hematological disease	0	142	135	0	0	5	282
2020	Liver disease	0	159	173	0	3	4	339
2020	Pregnant	0	158	179	5	1	5	348
2020	Immunosuppression	1	487	405	1	15	11	920
2020	Asthma	1	418	518	3	2	28	970
2020	Neurological disease	0	666	702	1	3	26	1398
2020	Kidney disease	0	583	853	3	4	5	1448
2020	Respiratory disease	1	726	883	1	10	14	1635
2020	Obesity	1	341	1383	1	1	5	1732
2020	Diabetes	2	1832	4982	8	11	15	6850
2020	Cardiovascular disease	3	2686	6829	11	13	22	9564
2020	Other comorbidities	6	3040	6389	13	32	54	9534
2021	Down Syndrome	1	29	110	0	0	4	144
2021	Postpartum	0	42	149	3	1	0	195
2021	Hematological disease	1	113	206	2	0	6	328
2021	Liver disease	0	125	271	5	1	1	403
2021	Pregnant	0	111	542	8	2	1	664
2021	Immunosuppression	0	286	548	7	5	22	868
2021	Asthma	1	294	798	22	1	41	1,157
2021	Neurological disease	1	542	967	11	5	34	1,560
2021	Kidney disease	2	391	1,191	5	7	4	1,600
2021	Respiratory disease	2	437	1,031	21	12	15	1,518
2021	Obesity	7	342	4,042	4	4	4	4,403
2021	Diabetes	12	1,409	8,418	30	16	11	9,896
2021	Cardiovascular disease	13	2,136	10,510	52	19	32	12,762
2021	Other comorbidities	9	2,314	13,308	45	24	101	15,801
2022	Down Syndrome	1	33	32	1	0	20	87
2022	Postpartum	0	13	27	1	0	2	43
2022	Hematological disease	0	91	94	3	2	5	195

2022	Liver disease	0	56	97	1	1	2	157
2022	Pregnant	1	45	73	7	1	3	130
2022	Immunosuppression	1	191	325	9	5	10	541
2022	Asthma	1	238	156	18	1	66	480
2022	Neurological disease	4	284	473	14	6	45	826
2022	Kidney disease	2	191	400	13	7	14	627
2022	Respiratory disease	2	316	413	31	4	23	789
2022	Obesity	0	153	305	14	2	5	479
2022	Diabetes	4	570	1,540	46	10	24	2,194
2022	Cardiovascular disease	4	880	2,060	76	20	82	3,122
2022	Other comorbidities	10	1,207	2,839	64	22	110	4,252
2023	Down Syndrome	2	10	4	2	0	11	29
2023	Postpartum	1	9	2	2	0	1	15
2023	Hematological disease	1	34	10	4	0	8	57
2023	Liver disease	0	10	9	1	0	2	22
2023	Pregnant	4	7	7	7	0	0	25
2023	Immunosuppression	6	63	33	8	0	13	123
2023	Asthma	15	92	25	12	0	25	169
2023	Neurological disease	8	66	42	17	0	17	150
2023	Kidney disease	3	44	33	4	0	2	86
2023	Respiratory disease	11	47	49	13	0	2	122
2023	Obesity	6	29	22	10	0	3	70
2023	Diabetes	33	83	123	16	0	5	260
2023	Cardiovascular disease	47	186	264	43	0	55	595
2023	Other comorbidities	35	160	148	40	0	32	415

Ferdinands, et al., analyzed patients from 8 hospitals in the United States of America (USA), with Influenza and acute respiratory illness [12]. Among its results, 93% of patients had at least one comorbidity that increased the risk of complications from the flu, the most common being cardiovascular diseases, diabetes and kidney disorders. In Brazil, 196,109 deaths resulting from SARS due to COVID-19 were reported between March 22, 2020 and June 30, 2021. Of these, 42% had cardiovascular diseases, 32% diabetes mellitus, 15% high blood pressure, 8% obesity and 6% lung diseases [13].

The study by Carvalho, et al., demonstrates similar results, with cardiovascular diseases and diabetes mellitus being the most prevalent risk factors among SARS cases due to COVID-19, corresponding to 37.8% and 31.5%, respectively, of the analyzed population [14].

Bernadi, et al., developed a study with patients hospitalized with SARS, around 72.2% of participants had at least one illness prior to the period of hospitalization, the most common being systemic arterial hypertension and type 2 diabetes mellitus [15].

According to the Pan American Health Organization/WHO, the groups most susceptible to complications associated with Influenza are children under two years of age, adults over 65 years of age, pregnant/postpartum women, people with clinical morbidity such as cardiovascular disease, diabetes, kidney, lung, neurological diseases and conditions of immunosuppression and obesity [16].

In Figure 1, the time series were plotted for SARS by COVID-19, Influenza, other viruses and total SARS regardless of the etiological agent. The current scenario is represented in blue, the adjustment is represented in red, the trend is represented in green and the forecast for the next 52 epidemiological weeks (13 months) or until June 2024, (Figure 1).

It is possible to observe the predicted reduction for COVID-19, starting from the 35th week. The estimate becomes negative with the forecast pointing to -2.9, whereas in the last forecast week the estimate was -83.7; the forecast is for a flattening or reduction in the number of SARS due to COVID-19. For Influenza, the forecast follows the seasonality of the 175 epidemiological weeks; with week 32 being the one with the highest predicted quantity, the predicted epidemiological week correspond to January 2024. When considering the scenario of the other viruses, epidemiological week 44 stood out with the forecast with the highest number of SARS cases. When considering the general scenario, it is possible to observe the influence of SARS due to COVID-19 on the scenario.

The Influenza virus causes seasonal and endemic epidemics and periodic pandemics [17]. In countries with a temperate climate, there are clear seasonal variations, with climate and humidity favoring the survival of the virus and weakening the host's immune system. In countries with a tropical climate, there are few temperature variations and humidity conditions predominate, making the existence of seasonality patterns difficult [18].

Brazil has an extensive continental dimension, with different latitudes and six climatic subtypes (equatorial, tropical, high-altitude tropical, subtropical, temperate and semi-arid), these aspects cause Influenza epidemic peaks to occur at different times in each region [19].

Oliveira demonstrated that the South, Southeast and Center-West regions of Brazil had a higher number of cases and deaths from Influenza between the months of March and August, while in the North region the peaks occur between February and May, meaning that even July for the Northeast region [20].

The data obtained from the 59 participants aged between 0 and 13 years present numbers proportionally similar to the data from the epidemiological weeks, however, the data collected allows a more specific analysis, highlighting other respiratory viruses, such as Parainfluenza and Rhinovirus (Figure 2).

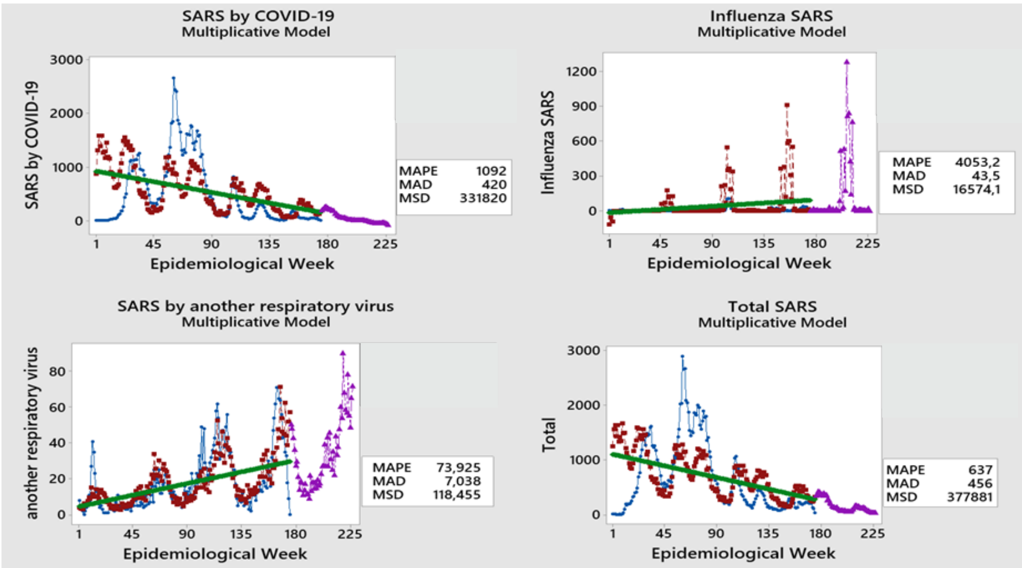

Figure 1: Time series: Curve fitting and SARS prediction for 52 epidemiological weeks. **Note:** (—■—): Actual; (—■—): Fits; (—◆—): Trend; (▲): Forecasts.

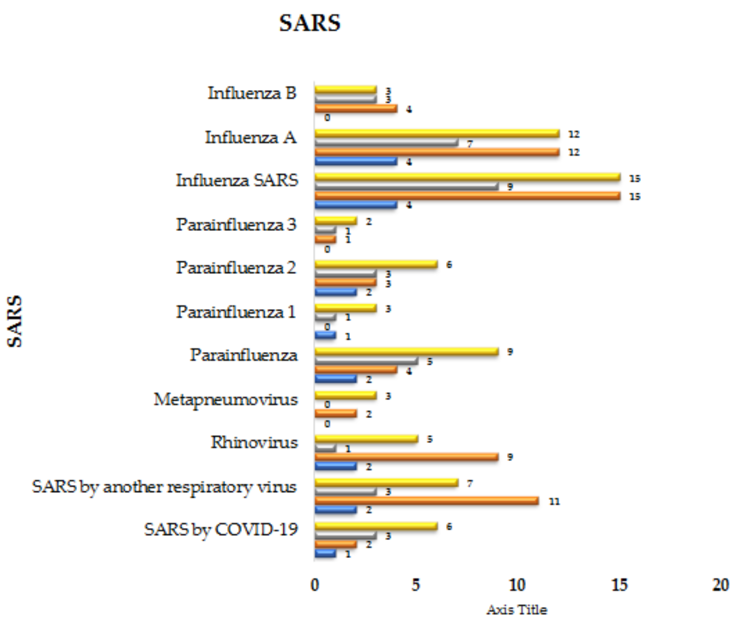

Figure 2: SARS by etiological agent. **Note:** (■): <2 years; (■); 5 to 9 years; (■): 2 to 4 years; (■): 10 to 13 years.

Of the 167,109 cases of SARS registered between 2020 and 2021 in northeastern Brazil, 63% were caused by COVID-19 and 37% were caused by other etiological agents or an unspecified cause [21].

In the study by Glória, et al., 1,366 SARS cases analyzed, 57.9% were closed as SARS due to COVID-19; the rest had no specified cause [22].

It was also possible to observe, through the data collected, the main signs and symptoms of the children analyzed, with 14 children having a cough, 13 children having a fevers, 11 children having a dyspenia and tachypnea and 9 children having a asthma. Other symptoms presented were: Nasal obstruction, diarrhea and abdominal pain, vomiting, loss of appetite. In total, two deaths were recorded (3.38%).

Second, Macías, et al., historical and more recent data show Influenza as a trigger for serious conditions, contributing to an increase in morbidity and mortality [23]. The São Paulo epidemiological bulletin published in 2022 presents children as a risk group for Influenza. Therefore, children under 2 years of age are at greater risk of hospitalization. Furthermore, children under 6 months of age have higher mortality rates [24].

The study by Sebben included 64 children aged 0 to 14 years with flu syndrome and diagnosis of Influenza A by PCR in oropharyngeal secretion [25]. The most common symptoms observed in children were fever, cough, tachypnea and intercostal and subcostal retractions. Furthermore, 20% of patients presented vomiting and/or diarrhea. Bett and colleagues would evaluate 1,169 patients aged 0 to 16 years with SARS due to Influenza [26]. The main clinical manifestations found by the authors were the association between fever, cough, dyspnea and respiratory discomfort. Therefore, fever, respiratory distress and admission to an Intensive Care Unit (ICU) demonstrated an association with death. This symptomatic picture was similar to that presented by the patients in the present study [9].

According to Harrington, et al., the Influenza virus presents known risks and constant genetic changes, posing a continuous threat to new emerging strains [27]. Given this, continuous investment must be made in the surveillance and coordination of research laboratories, risk assessment, vaccines and therapeutics. Furthermore, public health messages need to be clear and cohesive for the population.

CONCLUSION

Our results indicating that Influenza is among the most important agents of SARS in pediatrics. The observed epidemic period of respiratory infections can be useful for planning and implementing some prevention strategies.

Longitudinal studies should be carried out to confirm the results obtained in this medium-term study. Efficient strategies, such as the control of hospital infections caused by respiratory viruses, vaccination, rational use of antivirals and antibiotics, can be one of the many benefits generated by longitudinal studies of the clinical and epidemiological situation.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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