

Factors associated with Severe Acute Respiratory Syndrome in a Brazilian central region

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Abstract *Severe Acute Respiratory Infection (SARI) is a notifiable syndrome that must be investigated. This study aimed to analyze the epidemiological profile and factors associated with SARI-related hospitalization and deaths reported in Goiás. Retrospective cohort study, with data from the investigation files of the Notifiable Diseases Information System's Influenza Web. Multivariate analysis methods were employed to verify the association between exposure variables with the outcomes of ICU admission and death. A total of 4,832 SARI cases were reported in Goiás from 2013 to 2018. The primary etiological diagnosis was Influenza A (22.3%) with the predominant subtype A (H1N1pdm09), followed by the Respiratory Syncytial Virus. A total of 34.6% of the patients required ICU admission, and 19% died. A longer time to start treatment with antivirals was associated with a higher likelihood to have an ICU admission, while a previous non-vaccination against Influenza, longer time to start treatment, and older age were associated with a higher likelihood to suffer death. The study showed a high frequency of respiratory diseases caused by the Influenza virus in Goiás and that the severity of the syndrome, characterized by ICU admission and deaths, is associated with the start of antiviral treatment vaccine status, and patient's age.*

Key words *Human Influenza, Surveillance, Epidemiology, Severe Acute Respiratory Infection*

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Introduction

Severe Acute Respiratory Infection (SARI) is an infectious viral respiratory syndrome caused by influenza viruses and other etiological agents, such as the respiratory syncytial virus (RSV), parainfluenza, and adenovirus, which infect the upper respiratory tract¹. Patients have a flu-like condition associated with dyspnea or tachypnea (respiratory rate equal to or above 20 incursions per minute) or hypoxemia, with oxygen saturation (SpO_2) < 95% in room air².

It is a disease of epidemiological relevance that must be notified and investigated. The epidemiological monitoring of SARI in Brazil occurs through the epidemiological surveillance of the disease by completing notification forms through the Notifiable Diseases Information System (SINAN), and the operation of sentinel units. These units monitor SARI-related hospitalized cases and deaths to identify circulating respiratory viruses^{2,3}. Thus, all suspected SARI cases are hospitalized, notified, and investigated for the disease¹.

Epidemiological surveillance of SARI allows preventing and monitoring severe cases of the syndrome, identifying circulating viral types and subtypes, performing antigenic and genetic analysis of viruses, identifying new viral subtypes, monitoring resistance to antivirals and demand for care by disease, and controlling possible outbreaks, aiming at public health decision-making for its prevention and control⁴.

Globally, the circulation of influenza viruses remains high, and seasonal A virus is the most prevalent⁵. According to the epidemiological bulletin of the Ministry of Health⁶, Brazil has the same circulation profile, with the highest prevalence of the Influenza A H1N1 pandemic virus 2009 (H1N1pdm09). This scenario has recently changed with the new coronavirus pandemic, which started in late 2019 in China, with first Brazilian cases in early 2020⁷.

SARI can progress to complications, which lead to an increased risk of ICU admissions, mechanical ventilation, and even death⁸. Some factors are associated with a worse prognosis, such as the presence of chronic diseases, age extremes, viral strain, no previous vaccination, and use of antivirals 72 hours after the onset of symptoms, characteristics that should be investigated^{9,10}.

Thus, this study aimed to analyze the epidemiological profile and the factors associated with hospitalization and deaths from SARI in a central Brazilian region from 2013 to 2018.

Methods

This is a retrospective cohort study with data analysis regarding notified SARI cases and their progress during hospitalization in Goiás. Goiás is located in the Midwest region, with an area of 340,125,715 km², and is the seventh-largest Brazilian state in territorial extension. Its HDI ranks eighth in the country, at 0.735¹¹.

According to the definition of the Ministry of Health², all reported SARI cases in SINAN's Influenza Web, residing in the state of Goiás, regardless of age, were considered eligible for the study. The Ministry of Health defines SARI as the individual of any age with a flu-like syndrome (fever, cough, or sore throat, and at least one of the following symptoms: headache, myalgia, or arthralgia) associated with dyspnea or oxygen saturation $\text{SpO}_2 < 95\%$ ².

Data was collected on April 10, 2019. In 2012, a change was implemented in the notification form, and epidemiological surveillance directed the monitoring of Influenza by a new pandemic subtype for SARI. We decided to use 2012 data to ensure the performance of analyses with the same variables homogeneously. Thus, the data reported between 2013 and 2018 were collected.

This project was approved by the Research Ethics Committee linked directly to the "Leide das Neves Ferreira" Center for Excellence in Education, Research and Projects (GCEEPP-LNF) and the Research Ethics Committee linked to the Hospital das Clínicas of the Federal University of Goiás (UFG), and met the conditions established by Resolution MS/CNS 466/2012.

Data statistical analysis

Absolute and relative frequencies were obtained in the descriptive analysis according to each category under analysis (sociodemographic characteristics and data on the prevention, treatment, and development of the disease). Multivariate data analysis methods were used to verify the association between exposure variables and outcomes (deaths and ICU admission), and previous vaccination, use of antivirals, presence of the Influenza A/B virus, RSV, other respiratory viruses, treatment time in days, and age group, were considered variables of exposure.

Initially, a bivariate analysis was performed, testing the association of exposure variables with outcomes by calculating Odds Ratio (OR) and p-value. The variables whose association with the outcome was $p \leq 0.20$ were included in the mul-

tivariate logistic regression model. This model was progressively saturated with each variable's addition, observing its effects on the precision of the final model on the adjustment of the other variables for inclusion in the definitive model. The variables associated with the outcome finally showed a p -value < 0.05 . IBM SPSS Statistics software version 25.0 was used for statistical data analysis.

Results

A total of 4,832 SARI cases were reported in Goiás from 2013 to 2018. The highest percentage of notifications occurred in females (53.4%) and the 20-59 years' age group (45.8%). Other socio-demographic data are shown in Table 1.

Regarding the prevention, treatment, and development of the syndrome, only 20.7% of patients were previously vaccinated against Influenza, and 70.7% of them used antivirals. ICU admission was found in 34.6% of the cases, while 19% died (Table 1).

A predominance of Influenza A virus was observed throughout the study, followed by RSV. Influenza A virus (H1N1pdm09) was the predominant virus subtype. As for cases without etiology, defined as unspecified SARI, we observed 2,796 patients, which corresponds to approximately 58% of notifications, with an increase in notifications in 2016 and 2018. These same years recorded a significant increase in cases compared to other seasonal factors and, consequently, increased ICU admissions and deaths (Figure 1).

Table 2 shows the results of the bivariate and multivariate analyses between the exposure variables with the death outcome. In the bivariate analysis, a higher likelihood of death was observed in individuals who did not use antivirals, whose SARI was caused by Influenza A or B virus, with a higher number of days to start treatment, and older age. In the multivariate analysis, in turn, the variables use of antivirals, Influenza A or B infection, and RSV, lost association with the outcome, keeping the association between the time of onset of treatment and age group. A higher likelihood of death was also observed in the multivariate analysis in individuals who had not previously been vaccinated against Influenza.

For the outcome of ICU admission, in the bivariate analysis, the non-use of antivirals, infection by Influenza A or B, RSV, and other respiratory viruses reduced the likelihood of ICU admission. At the same time, the longer time to

start treatment increased the likelihood of this complication. In the multivariate analysis, the variables infection by Influenza A or B and RSV continued to be negatively associated with the outcome, while the time to start treatment remained positively associated with the outcome (Table 3).

Discussion

This study allowed observing SARI notifications in the state of Goiás for six years. Analyzing the confirmed cases' sociodemographic characteristics, we observed no significant difference regarding gender, unlike studies carried out in New Zealand, the U.S., and France, in which females were predominant¹²⁻¹⁶. Regarding the age group, the largest number of people affected was aged between 20 and 59 years, a group that is not part of the indication for vaccination against Influenza by the Brazilian Ministry of Health. A high frequency of cases was also observed in groups considered to be at higher risk, children under five years old (28.6%) and older adults above 60 years (15.0%), as seen in other studies^{12,17,18}. In the literature, individuals at extreme ages are at higher risk for respiratory conditions, such as Influenza and pneumonia^{19,20}.

Brazil has one of the most extensive immunization programs globally, with a considerable volume of doses administered against various diseases, and is provided free of charge²¹. Among these vaccines is the one against Influenza, incorporated in the National Vaccination Program (PNI) in 1999²², which is made available free of charge to risk groups nationwide, among them: children aged six months to under six years of age, pregnant women, puerperae, and patients with NCDs. In this study, we observed that 59.1% of the SARI individuals had not received previous vaccination against Influenza. It is worth mentioning that the largest number of cases in our study is in the age group not covered by vaccination provided by the PNI. While not provided to the entire population through the SUS, influenza vaccination is available in the private health network. It is essential to highlight that influenza vaccination, as a public health measure, reduces hospitalizations, especially in people at risk (children under five, older adults, and pregnant women)²³. However, several factors influence the vaccine's effectiveness, such as the compatibility of the circulating strains with the vaccine strains, the individual's immune response, and previous

Table 1. Sociodemographic characteristics of patients with SARI notified in Goiás and characteristics related to the prevention, treatment, and development of the disease, 2013-2018 (n=4.832).

Characteristics	N	%
Gender		
Male	2,250	46.6%
Female	2,581	53.4%
Unknown	1	0.0%
Age group		
0-5 years	1,381	28.6%
6-19 years	512	10.6%
20-59 years	2,213	45.8%
60 years and over	724	15.0%
Unknown	2	0.0%
Pregnancy		
1° trimester	47	1.0%
2° trimester	104	2.2%
3° trimester	125	2.6%
Unknown gestational age	5	0.1%
No	1,236	25.6%
Not applicable	3,147	65.1%
Unknown	168	3.5%
Skin color		
White	1,471	30.4%
Black	235	4.9%
Yellow	53	1.1%
Brown	2,438	50.5%
Indigenous	5	0.1%
Unknown	630	13.0%
Schooling		
No schooling	110	2.3%
Elementary School	809	16.7%
Secondary School	800	16.6%
Higher Education	311	6.4%
Not applicable	1,423	29.4%
Unknown	1,379	28.5%
Prevention, treatment and evolution		
Prior vaccination		
Yes	998	20.7%
No	2,854	59.1%
Unknown	980	20.3%
Use of antivirals		
Yes	3,416	70.7%
No	1,203	24.9%
Unknown	213	4.4%
Hospitalization		
Yes	4,797	99.3%
No	30	0.6%
Unknown	5	0.1%

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Table 1. Sociodemographic characteristics of patients with SARI notified in Goiás and characteristics related to the prevention, treatment, and development of the disease, 2013-2018 (n=4.832).

Characteristics	N	%
ICU admission		
Yes	1,670	34.6%
No	2,969	61.4%
Unknown	193	4.0%
Development		
Discharge	3,740	77.4%
Death	920	19.0%
Unknown	172	3.6%

ICU = Intensive Care Unit.

vaccination by the same strain of the current vaccine^{24,25}.

With a suspected disease, all patients should start antiviral treatment as early as possible, even without the etiological identification². Antiviral administration can reduce the duration of symptoms, viral load, and the transmission capacity²⁶. Failure to use antivirals or inappropriate use (more than 48 hours after the onset of symptoms) is associated with virus infection complications, such as aggravation followed by ICU admission and progression to death⁸. The non-use of the medication was observed in 24.9% of patients in this study. Thus, it is necessary to strengthen actions for the proper management of patients with SARI as a strategy to reduce severe cases of this disease.

We observed that the influenza virus is the most prevalent etiological agent, followed by RSV. A higher frequency of virus A (H1N1pdm09) was noted among the influenza viruses, followed by A (H3N2) and the influenza B virus. Year-to-year variations were observed for both pathogens, which may be due to different strains and circulation patterns of viruses at every season²⁷, and highlights the importance of estimating the disease burden associated with virus infection and strengthening surveillance actions in the epidemiological investigation of the syndrome, which corroborates public health measures^{4,28}. This same viral circulation pattern is observed in other studies, where A viruses (H1N1pdm09) represent the majority of identified viruses²⁹⁻³¹.

It is interesting to note a significant increase in SARI cases in the state of Goiás in 2016 and 2018, which may be because vaccination cov-

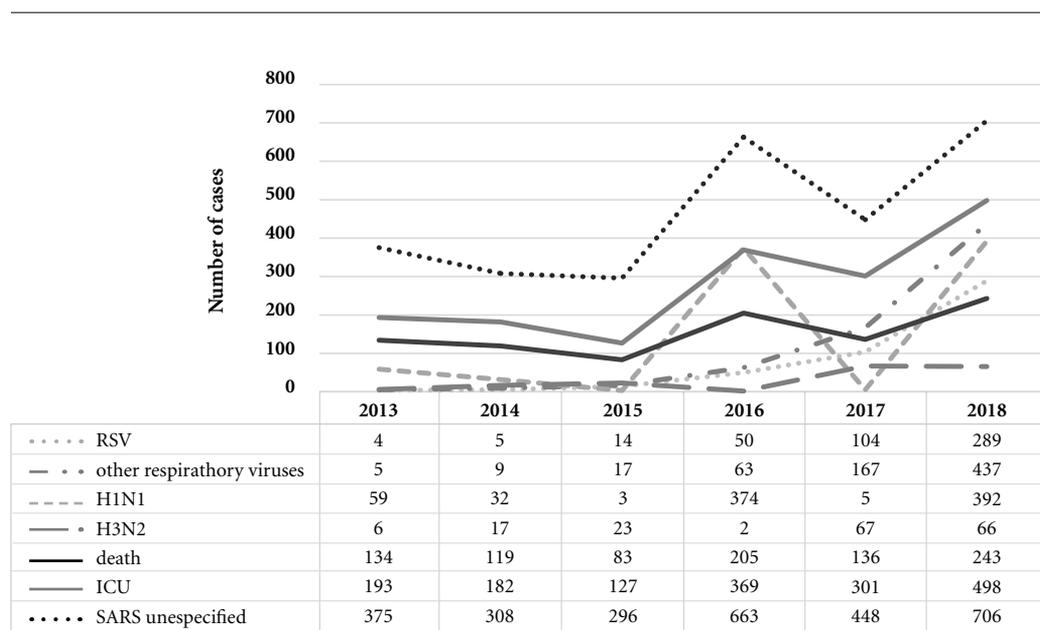


Figure 1. Temporal evolution of deaths and hospitalizations in ICU due to SARI in Goiás and the number of cases according to etiological diagnosis, 2013-2018.

RSV = Respiratory Syncytial Virus; ICU = Intensive Care Unit.

erage for some specific groups, such as patients with comorbidities, was below the 90% target in previous years (2015 and 2017), favoring higher viral circulation in the following seasons.

Identifying the influenza virus in symptomatic patients is associated with an increased risk of respiratory complications, represented by deaths and ICU admission, besides other contributing factors, such as the patient's age, viral strain, vaccine status, and antiviral use²⁷. Our study observed that 19% of patients died, and 34.6% were admitted to the ICU, as seen in other studies^{8,32}. Also, we observed that the likelihood of having a severe outcome (death and ICU admission) was higher in young adults or older adults than children, in those who had not previously been vaccinated against Influenza and with a higher number of days to start antiviral treatment. According to Naudion et al.³³, this virus is the most associated with the complications of the syndrome and, likewise, the non-use of antivirals and the absence of immunization are related to

the complications³³. Other studies indicate that patients who used antivirals and had previous vaccination for Influenza had a significant reduction in the risk of complications^{19,22}. Regarding the age group, studies in the literature have also shown a higher likelihood of complications at older ages^{8,33}.

As a limitation of the study, we can highlight that the frequency of cases and deaths due to SARI can be underestimated due to their passive notification and the sensitivity of health professionals in identifying suspected cases. Underreporting of cases in the SINAN should not occur, as SARI is mandatory for health surveillance³⁴. The number of unidentified cases, but capable of transmitting the disease, is a critical epidemiological characteristic that modulates the potential for the spread of the virus³⁵. Another downside is the use of secondary data, which can sometimes be incomplete and with limitations on variables. Thus, local surveillance levels should be trained and make extensive use of data from information

Table 2. Factors associated with death by SARI cases notified in Goiás, 2013 to 2018.

Characteristics	Death		Bivariate logistic regression				Multivariate logistic regression			
	Yes (n=920)	No (n=3740)	Unknown (n=172)	OR	95%CI	P	OR	95%CI	P	
Vaccine										
No	391	2353	110	1.19	0.96-1.49	0.117	1.49	1.10-2.03	0.011	
Yes	118	847	33	ref	-	-	ref	-	-	
Unknown	411	540	29							
Antiviral										
No	298	857	51	1.83	1.56-2.15	<0.001	2.54	0.63-10.21	0.189	
Yes	528	2784	103	ref	-	-	ref	-	-	
Unknown	94	99	18							
Influenza A or B										
Positive	275	884	32	1.36	1.15-1.60	<0.001	1.17	0.89-1.54	0.247	
Negative	550	2401	56	ref	-	-	ref	-	-	
Unknown	95	455	84							
RSV										
Positive	29	429	8	0.25	0.17-0.36	<0.001	0.73	0.41-1.30	0.285	
Negative	746	2706	73	ref	-	-	ref	-	-	
Unknown	145	605	91							
Other respiratory viruses										
Positive	69	617	12	0.41	0.32-1.01	0.462	-	-	-	
Negative	840	3112	86	ref	-	-	ref	-	-	
Unknown	11	11	74							
Treatment start time										
0-2 days	145	1091	48	ref	-	-	ref	-	-	
3-5 days	189	991	32	1.43	1.13-1.81	0.002	1.4	1.02-1.91	0.035	
6-8 days	110	402	11	2.06	1.57- 2.70	<0.001	1.99	1.38-2.88	<0.001	
9 days and over	74	268	11	2.08	1.52-2.8	<0.001	1.73	1.13-2.66	0.012	
Unknown	402	988	70							
Age group										
0-5 years	116	1213	52	ref	-	-	ref	-	-	
6-19 years	63	432	17	1.52	1.10-2.11	0.011	1.09	0.59-2.01	0.776	
20-59 years	507	1625	81	3.26	2.63-4.04	<0.001	2.49	1.65-3.76	<0.001	
60 years and over	234	468	22	5.23	4.08-6.69	<0.001	5.21	3.29-8.26	<0.001	
Unknown	0	2	0							

RSV=Respiratory Syncytial Virus.

Table 3. Factors associated with the ICU admission for SARI cases notified in Goiás, 2013 to 2018.

Characteristics	ICU admission		Bivariate logistic regression				Multivariate logistic regression*			
	Yes (n=1670)	No (n=2969)	Unknown (n=193)	OR	95%CI	p	OR	95%CI	p	
Vaccine	No	1890	90	1.01	0.86-1.18	0.938	-	-	-	
	Yes	655	42	ref	-	-	ref	-	-	
	Unknown	424	61							
Antiviral	No	789	42	0.83	0.72-0.95	0.009	0.7	0.18-2.74	0.611	
	Yes	2109	94	ref	-	-	ref	-	-	
	Unknown	71	57							
Influenza A or B	Positive	761	40	0.79	0.68-0.91	0.001	0.79	0.65-0.95	0.014	
	Negative	1756	111	ref	-	-	ref	-	-	
	Unknown	452	42							
RSV	Positive	331	11	0.57	0.46-0.71	<0.001	0.56	0.41-0.75	<0.001	
	Negative	2050	124	ref	-	-	ref	-	-	
	Unknown	588	58							
Other respiratory viruses	Positive	462	15	0.82	0.67-1.06	0.02	0.69	0.55-1.32	0.06	
	Negative	2460	156	ref	-	-	ref	-	-	
	Unknown	47	22							
Treatment start time	0-2 days	861	38	ref	-	-	ref	-	-	
	3-5 days	744	31	1.31	1.11-1.55	0.002	1.27	1.04-1.55	0.019	
	6-8 days	276	15	1.88	1.52-2.32	<0.001	1.94	1.51-2.49	<0.001	
Age group	9 days and over	200	9	1.61	1.26-2.05	<0.001	1.53	1.14-2.06	0.005	
	Unknown	888	100							
	0-5 years	875	37	ref	-	-				
6-19 years	6-19 years	307	18	1.14	0.92-1.41	0.241				
	20-59 years	1345	104	1.06	0.92-1.22	0.427				
	60 years and over	440	34	1.06	0.87; 1.28	0.551				
Unknown	0	2	0							

* Collinearity statistics: tolerance > 0.1 and VIF < 10; Hosmer-Lemeshow Test: p = 0.167; Nagelkerke R² = 0.032; RSV = Respiratory Syncytial Virus.

systems to identify weaknesses and inconsistencies in the data, improve the quality of the systems, and make them effective³⁴.

SINAN and other Health Information Systems of the Brazilian Ministry of Health are a valuable source of health information that assists in planning health policies and programs, collaborating in the decision-making process, besides allowing assessment of the impact of interventions. Thus, even in the face of limitations, they are essential tools for public health and, especially, for disease epidemiological surveillance. Also, with the new coronavirus pandemic in the country in 2020, the SARI surveillance system is being

strengthened and is an essential step for public health concerning the epidemiological and laboratory surveillance of respiratory agents.

Conclusion

Several cases of respiratory diseases caused by the Influenza virus and other etiological agents occur in the state of Goiás, and we observed that the severity of the syndrome, characterized by ICU admission and deaths, is associated with the patient's age, start time to treatment with antivirals, and vaccination status.

Collaborations

KLR Araujo and YMF Ternes participated in the conception, design and writing of the article. EC Aquino, LLS Silva and YMF Ternes participated in the statistical analysis and interpretation of the data. All authors participated in the critical review and approval of the version to be published.

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