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Original Article

Not all respiratory infections were SARS-CoV-2 during the pandemic, analysis in a clinic on the Colombian Caribbean coast



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ABSTRACT

Introduction: Acute Respiratory Infections (ARIs) are considered one of the leading causes of morbidity and mortality worldwide. Children under five and older adults are most likely to die from this cause. *Objective:* To describe the behavior of infection by respiratory viruses other than SARS-CoV-2 during the pandemic in a clinic in the Colombian Caribbean.

Methods: This descriptive and retrospective study evaluates the characteristics, associated comorbidities, and requirements of hospitalization or Intensive Care Unit in patients diagnosed with respiratory viral infections treated at IMAT Oncomedica clinic from July 2020 to August 2022.

Results: This study evaluated 351 patients with respiratory symptoms, observing an exponential increase in cases of respiratory infection as of April 2022, with a high proportion of syncytial virus infections mainly in children under 18 years of age (22.1%) and Human Rhinovirus/Enterovirus in patients with solid tumors and hematological disorders (48.8%), the latter was associated with a higher rate of hospitalization and ICU requirement in the individuals evaluated.

Conclusions: Respiratory viruses other than SARS-CoV-2, such as Rhino/Enterovirus, RSV, and adenovirus, are circulating in the population at a clinic on the Colombian Caribbean coast. The findings should motivate public health authorities to conduct more thorough surveillance in the rest of the state.

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Introduction

Acute Respiratory Infections (ARIs) are considered one of the leading causes of morbidity and mortality worldwide. Children under five and older adults are most likely to die from this cause. In Colombia, ARIs are the fifth leading cause of mortality in the general

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population and is among the top three causes in children under five years of age. Historically, the behavior of acute respiratory infections in Colombia presents two periods where the increase in the frequency of consultations and hospitalizations is evident. The first is observed between May and June, and the second between September and December. During the pandemic, it is unknown whether this epidemiological pattern has changed [1]. The World Health Organization (WHO) declared COVID-19 a global pandemic on March 11, 2020. In Colombia, 13 days later, social activities, free mobility, and the closure of schools and universities, among others, were restricted [2]. The measures appear to reduce the prevalence of respiratory virus infections other than COVID-19, such as influenza and Respiratory Syncytial Virus (RSV) in 2020 [3]. However, during the pandemic, it was a cause of concern to observe that respiratory

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Abbreviations: ARIs, Acute respiratory infections.; WHO, World Health Organization; RSV, Respiratory syncytial virus; ICU, Intensive care unit; PAHO, Pan American Health Organization

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Fig. 1. Flowchart of admitted patients in the study.

infections other than SARS-CoV-2 continued to exist in some medical centers in Colombia. Although the SARS-CoV-2 variant Omicron continues to circulate in Colombia, influenza and respiratory virus season has been influenced by the La Niña weather phenomenon that has increased rainfall [4]. That implies a cocirculation of respiratory viruses other than SARS-CoV-2. It is unknown whether coinfection increases the severity of the disease compared to that associated with infection by a single virus. On the other hand, in Colombia, vaccination against COVID-19 until December 2022 was 71% with a complete protocol and 12% partially vaccinated [5], but there is no strict monitoring of vaccination against influenza and Bordetella. Focusing on detecting SARS-CoV-2 may neglect other etiological agents of ARIs. This research aims to describe the behavior of infection by respiratory viruses other than SARS-CoV-2 during the pandemic in a clinic in the Colombian Caribbean.

Materials and methods

Population, type of study, and sample

The present work is a descriptive and retrospective study that evaluates the clinical characteristics, associated comorbidities, and requirement of hospitalization or Intensive Care Unit in patients diagnosed with respiratory viral infections attended to and treated at the IMAT Oncomedica clinic from July 2020 to August 2022. The inclusion criteria of this research were patients with respiratory signs or symptoms (cough, rhinorrhea, odynophagia, headache, malaise, nasal congestion, fever) who were treated on an outpatient basis or admitted to hospitalization ICU. Fourteen thousand oropharyngeal swabs with viral transport medium were analyzed during the study period. The high number was due to the epidemiological situation of COVID-19 that required studying symptomatic respiratory patients. Of the 14,000 specimens, through convenience sampling, 351 patients were chosen consecutively (Fig. 1-Flowchart). Non-probability sampling was conducted to know the circulation of viruses other than SARS-CoV-2. Patients with no respiratory signs or symptoms and those whose medical history did not have clinical and demographic information more outstanding than 10% in the primary study variables were excluded.

Site of study and laboratory diagnosis

This study was conducted in the department of Córdoba, located northwest of the Colombian Caribbean coast, with a population of 1785,000 inhabitants. The capital of the department is Monteria, with a population of 505,000. The study was conducted in the city's largest private third-level clinic. It is a multipurpose clinic specializing in the comprehensive care of managing patients with oncohematological diseases. The clinic has a molecular biology laboratory; manual tests are performed for SARS-CoV-2 (RT-qPCR). Also, BioFire® FilmArray Respiratory PCR Panel 2.1 (BioFire RP2.1, BioFire Diagnostics, bioMérieux, Marcy l'Etoile, France) are performed. BioFire RP2.1 is a multiplex PCR allowing the simultaneous detection of four bacteria (B. parapertussis, B. pertussis, C. pneumoniae, M. pneumoniae) and 19 viruses (Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, SARS-CoV-2, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza A/H1, Influenza A/H3, Influenza A/H1-2009, Influenza B, Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus, Parainfluenza Virus 4, Respiratory Syncytial Virus).

Ethical aspects

The Institute of Tropical Biological Research investigation committee of the University of Cordoba Colombia permitted the ethics protocol. Patients were anonymized using a numeric code. The study incorporated procedures, management and conservation of samples, and technical-administrative procedures for health research required by resolution 8430 of the Ministry of Health of Colombia in 1993 and the declaration of Helsinki for ethical and medical research in human subjects.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences version 27 (IBM, Armonk, NY, USA). The univariate analysis for the qualitative variables was carried out by calculating absolute and relative frequencies. Bivariate analysis of the qualitative and quantitative variables was carried out with the chi-square test. The

Table 1

Clinical characteristics of studied patients.

Characteristic patients evaluated (N = 351)		
Sex (%)	Female	157 (44.7)
	Male	194 (55.3)
Median age in years (range)		15 (0-87)
Comorbidities (%)	Solid tumors or hematological disorders	75 (21.3)
	Arterial hypertension	31 (8.8)
	Diabetes mellitus	16 (4.5)
Influenza vaccination (%)	Yes	92 (26.1)
Film array Result (%)	Detected	206 (58.7)
	Not detected	145 (41.3)
Detected microorganism (%)	Human Rhinovirus/Enterovirus	61 (29.6)
	Coinfections	43 (20.9)
	Respiratory Syncytial Virus	34 (16.5)
	Human Metapneumovirus	11 (5.3)
	Coronavirus 229E	10 (4.9)
	Adenovirus	9 (4.4)
	Influenza AH3	8 (3.4)
	Other microorganisms	30 (15)
Coinfections (%)	Coinfections deteted	43/351 (12.2)
	Two microorganisms detected	33 (76.7)
	≥ three microorganisms detected	10 (23.3)
Main coinfections (%)	Human Rhinovirus/Enterovirus +Respiratory Syncytial Virus	9 (27.3)
	Human Rhinovirus/Enterovirus +Respiratory Syncytial Virus + Adenovirus	3 (30)
Clinical managment (%)	Ambulatory	155 (75.2)
	Hospitalization	24 (11.7)
	ICU	20 (9.7)

significance of the p-value was established at < 0.05 for all the analyses carried out.

Results

Three hundred fifty-one patients were evaluated, of which 55.3% were men, with a mean age of 15 years, and 41.5% were in an age range between 0 and 9 years. In 206 patients (58.7%), the causative agent of respiratory infection was detected. Only 15% of patients had a single infection, 76.7% had two microorganisms, and 23.3% had three (Table 1).

The most frequent viruses detected were human Rhinovirus/ Enterovirus (29.6%), RSV (16.5%), and coinfections with more than two microorganisms (20.9%). Coronavirus 229 E was detected in 10 patients (4.9%), the coronaviruses NL63, OC43 were also detected. (Table 2). From the clinical point of view, 21.3% of patients had some solid tumor or hematological disorder as comorbidities, and 26.1% had been vaccinated against Influenza. 21.4% of patients evaluated

Table 2

Relationship between age range (under 18 years vs. over 18 years) with the type of microorganisms detected.

Microorganism	Age range		P-value
	< 18 years	≥ 18 years	
Coinfection	34 (79.1)	9 (20.9)	< 0.0001
B. parapertussis	0	2 (100)	0.66
Human Rhinovirus/Enterovirus	36 (63.2)	21 (36.8)	< 0.0001
Parainfluenza virus 4	2 (50)	2 (50)	0.317
Adenovirus	7 (77.8)	2 (22.2)	0.042
SARS-CoV-2	1 (100)	0	1
Coronavirus NL63	0	4 (100)	0.4
Coronavirus 229E	3 (30)	7 (70)	0.016
Respiratory Syncytial Virus	31 (91.2)	3 (8.8)	< 0,0001
Parainfluenza virus 3	4 (66.7)	2 (33.3)	0.126
Coronavirus OC43	0	6 (100)	0.017
Influenza A H3	5 (62.5)	3 (37.5)	0.038
Influenza A	4 (66.7)	2 (33.3)	0.126
Human Metapneumovirus	11 (100)	0	0.002
Parainfluenza virus 1	1 (100)	0	1
Parainfluenza virus 2	2 (100)	0	0.665
TOTAL	141	63	< 0,0001

required hospitalization or management in an intensive care unit (Table 1).

Cases of respiratory infection over time

Cases of respiratory infection between 2020 and 2022 showed an exponential increase from April 2022. Since April 2022, there has been a 38.5% increase in respiratory infection cases treated at the study site compared to 2021 (Fig. 2A). On the other hand, influenza cases peaked in December 2021 and decreased from January to June 2021. As of July 2021, influenza cases increased exponentially (Fig. 2B).

Microorganisms found in pediatric and adult patients

Respiratory Syncytial Virus infection proportion was higher among those younger than 18 (22.1% < 18 years vs. 6.3% > 18 years). In addition, a high rate of coinfections and infections by Human Rhinovirus/Enterovirus was observed in both age ranges (Fig. 3A-Table 2).

Relationship between solid neoplasms or hematological disorders with the type of microorganisms detected other than SARS-CoV-2

A higher proportion of respiratory infections by Human Rhinovirus/Enterovirus (48.8%) was evidenced in individuals with solid tumors or hematologic disorders. While in individuals without these pathologies, a higher proportion of respiratory syncytial virus infections (31%) and coinfections (27.6%) was observed (Fig. 3B).

Type of microorganisms, hospitalization cases, and Intensive Care Unit (ICU) in individuals with and without solid neoplasia or hematological disorders

It was evidenced that Human Rhinovirus/Enterovirus infections and coinfections were related to the need for hospitalization and admission to the ICU between 2020 and 2022 (Fig. 4).



Fig. 2. A Cases with respiratory infection in the study clinic, August 2020 -August 2022. Cases of respiratory infection between 2020 and 2022 showed an exponential increase from April 2022. Fig. 2B Cases with respiratory infections by Influenza Virus, August 2020 -August 2022. influenza cases peaked in December 2021 and decreased from January to June 2021. However, in July 2021, influenza cases increased exponentially.

Discussion

In the present study, we found a higher prevalence of respiratory viral infections in the pediatric population; 41.5% were children between 0 and 9 years. As the literature describes, infections significantly cause morbidity and mortality in cancer patients [1,6].

Among the comorbidities associated with respiratory viral infections, a higher prevalence was detected in patients with hematological and oncological diseases. Infections significantly cause morbidity and mortality in cancer patients [6]. In 58.7% of patients, it was possible to detect the causative agent of respiratory infection; 43 patients were detected with coinfection, 76.7% had two microorganisms, and 23.3% had three microorganisms (Table 1). Only 15% of patients had a mono-infection. In patients with coinfections and oncological disease, all were managed in the ICU, while in patients without cancer, the highest percentage was managed in hospitalization rooms. It has been described in the pediatric population that respiratory viral coinfections would not influence more significant morbidity, hospital stay, or need for ICU and mechanical ventilation [7].

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Fig. 3. A-B. Proportion of respiratory virus infections by age range and presence of tumor pathologies or solid tumors. 2 A. Respiratory Syncytial Virus infection proportion was higher among those younger than 18 years. 2B. A higher proportion of respiratory infections by Human rhinovirus/enterovirus was evidenced in individuals with solid tumors or hematologic disorders.

The region where the study was conducted is a tropical area with dry and rainy seasons [8]. However, we have been experiencing the La Niña weather phenomenon for seven months [4]. In the study period, a significant increase in cases of ARI was evidenced in April, which has a relationship with the rainfall in the city. However, as seen in Fig. 1, respiratory virus activity is usually present throughout the year, like in the rest of the country, despite environmental factors and climate change [1]. In the tropics, the climatic effects do not seem to affect the circulation of respiratory pathogens, but their incidence does.

In Colombia, according to data reported by the National Institute of Health, surveillance of ARI between epidemiological weeks 1–14 April 2022 predominated RSV and adenovirus infections [1]. In epidemiological studies in the pediatric population < 5 years of age, from large cities of Colombia such as Cali, Medellín, Manizales, Bogotá, Tunja, Bucaramanga, and Cartagena, RSV was found as the most frequent and evidencing that the periodicity of RSV in the year has peaks that vary according to the city and rainy season [9]. Our study found that the most frequently detected virus was Human Rhinovirus/Enterovirus, followed by coinfections and RSV. The behavior of Rhinovirus/Enterovirus is evidenced as a frequent cause of upper and lower respiratory infections, especially in immunocompromised patients [10]. A retrospective study of pediatric cancer patients identified similarities in seasonal patterns of viral infections with and without cancer. Rhino/enterovirus was detected more frequently in both groups in spring, summer, and autumn. However, in the winter, influenza was more common, while RSV was the most common in patients without cancer [11]. An "unexpected persistence" of the prevalence of Rhinovirus/Enterovirus infections during the COVID-19 pandemic in Canada [12] was described, in the same way, the behavior of Rhinovirus/Enterovirus as the primary cocirculating virus with SARS-CoV-2 is described in two hospitals in Porto Alegre, Brazil [13].

We highlight the low activity of influenza viruses during the first period of this study and an increase in cases, specifically influenza A H3 at the end of 2021, as evidenced by data reported in FluNet [14]



Fig. 4. Type of organisms, hospitalization cases and Intensive Care Unit in individuals with and without solid neoplasm or hematological disorders. This figure shows that Human Rhinovirus/Enterovirus infections and coinfections were related to the need for hospitalization and admission to the ICU between 2020 and 2022.

and Pan American Health Organization (PAHO) Influenza situation reports, observing according to the report for the Andean countries that influenza activity remained low, with a predominance of influenza A(H3N2) and concurrent circulation of influenza B/Victoria. Overall, SARS-CoV-2 activity was low in the subregion, while RSV activity increased in our country [15]. Itaya et al. [16] concluded that the COVID-19 pandemic could have altered health behaviors, unexpectedly reducing seasonal influenza cases.

On the other hand, in Colombia, 6,363,544 patients have been diagnosed with COVID-19 by the laboratory. In Córdoba, only 122.316 people were diagnosed during the study period, with a clear underreporting of cases [17]. The increase in respiratory infections

by RSV and adenovirus as of May 2022 would be explained by the fact that 71% of the inhabitants of this region have a complete vaccination schedule against SARS-CoV-2 [5]. In addition, in this area of the Colombian Caribbean, more than half of the population has been naturally infected with SARS-CoV-2, with INS reports of approximately 63,265 confirmed cases and 1873 deaths [18], which would explain having a good humoral and cellular hybrid response to this virus.

The exponential increase in respiratory infections caused by other viruses could also be related to eliminating of sanitary measures as of April 2022 by the Colombian Ministry of Health. The ministry abolished the mandatory use of masks in open spaces and

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restrictions on capacity in educational and commercial centers [19]. In addition, frequent hand washing, a simple and valuable hygiene measure in controlling these respiratory infections, was abandoned.

It is alarming the low percentage of vaccination of the general and oncological population against influenza. In our study, it was evidenced in 26.1%, far from the coverage of vaccination against influenza in Colombia for the year 2021, reported of 84.8% for the first dose in the population of 6–11 months of 85% of 12–23 months, in people over 60 years of age it is 70.5% and in pregnant women 71.3% [20].

No data were collected on associated outcomes, especially in the oncological population, so this study lays the foundation for future research to help discern whether respiratory viral infections, especially by some viruses such as Human Rhinovirus/Enterovirus, have a much more torpid behavior in patients with hematological diseases than in the immunocompetent population. Although our study was in the most significant private clinic in the city, it has the limitation of having a single epidemiological horizon.

The type of non-probabilistic sampling of the present study does not allow the results to be extrapolated to the entire capital. Nevertheless, the results provide information hitherto unknown in the country and encourage promoting vaccination in the immunocompromised population and insisting on the importance of not abandoning the frequent use of masks and frequent hand hygiene.

In conclusion, respiratory viruses other than SARS-CoV-2, such as Human Rhinovirus/Enterovirus, RSV, and adenovirus, are circulating in the population at a clinic in the Colombian Caribbean. The findings should motivate public health authorities to conduct more thorough surveillance in the rest of the department and the Caribbean region, Colombia.

Ethical approval

This research was approved by the ethics and research committee of Oncomedica S.A.

Ethical aspects

Consent for patients' treatment was obtained and categorized privately. The work was endorsed by the Ethics Committee of the Institute of Biological Research of the Tropics (IIBT) of the University of Córdoba and the IMAT Clinic. The study was under the strict international ethical standards of the World Health Organization and the National Pan-American Health Organization. In addition, the study was supported by the Declaration of Helsinki and Colombia resolution 008430 of 1993 of the Ministry of Health of Colombia.

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CRediT authorship contribution statement

MJGP: Study design, Data collection, Manuscript Writing – original draft preparation, Writing – review & editing. **HJCD:** Study design, Writing – review, & editing. **APND:** Data collection. **JDCV:** Writing – eview & editing of the manuscript. **MCS:** Writing – eview & editing of the manuscript. **HCS:** Data analysis, Manuscript Writing – original draft preparation. **SM:** Study design, Manuscript Writing – original draft preparation, Writing – review & editing.

Declaration of Competing Interest

None declared. All authors read and approved the manuscript.

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