

Wheezing and asthma epidemiology in infants and preschoolers

Situación epidemiológica de la bronquitis obstructiva y asma en lactantes y preescolares

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What do we know about the subject matter of this study?

The hospitalization rate due to asthma in Chilean children aged 5 to 15 years is 7.8 per 10,000 inhabitants, with a significant increase observed between 2001 and 2014. Mortality in this age group is 0.37 per 100,000 inhabitants.

What does this study contribute to what is already known?

The hospitalization rate due to asthma in Chilean children under 5 years of age is 7.6 per 10,000 inhabitants. A significant increase in this rate was observed between the years 2002 to 2017. There was no mortality due to asthma in the studied period.

Abstract

In Chile, there is a lack of information about wheezing and asthma epidemiology in children under 5 years of age. **Objective:** To determine at the national level the hospitalization and mortality rates in children aged under 5 years with diagnosis of acute bronchitis and asthma. **Patients and Method:** Hospitalization rates were made using discharge data provided by the Department of Health Statistics and Information, selecting only those corresponding to the ICD10 codes for asthma and acute bronchitis. Population sizes of those at risk of hospitalization were obtained from projections of the National Institute of Statistics. The mortality rate was obtained by calculating the quotient between the number of deaths due to acute bronchitis and asthma in children under 5 years of age and the exposed population. The evolution of the global and regional hospitalization rates from 2002 to 2017 was studied. **Results:** Most of the patients who were hospitalized had a diagnosis of acute bronchitis (93,6%), were under two years old, were male, and were hospitalized in winter. During the analyzed period, the acute bronchitis hospitalization rate dropped from 79.7 to 56.1 per 10,000 inhabitants, meanwhile, the asthma hospitalization rate increased from 2.4 to 7.6 per 10,000 inhabitants. The mortality rate in patients with acute bronchitis was 0.52 per 100,000 inhabitants. No mortality was observed in patients diagnosed with asthma. **Conclusions:** During the analyzed period, a significant reduction in hospitalization rate due to acute bronchitis was observed in children aged under 5 years, with a low mortality rate.

Keywords:

Asthma;
Wheezing;
Hospitalization;
Mortality;
Preschoolers;
Infants

Introduction

Between the years 2001 to 2014, there was a significant increase in hospitalization rates due to asthma in Chilean school-aged children, reaching 7.8 per 10,000 inhabitants in 2014¹. The mortality rate due to asthma in this age group is 0.37 per 100,000 inhabitants, which is very similar to the one observed in developed countries such as the United States². In Chile, there has been great progress in the knowledge of the epidemiology of bronchial asthma in school children; however, there is still unawareness of the situation in children under 5 years of age.

We know that most patients with asthma start their symptoms during the first years of life; however, it is very difficult to certify the diagnosis of asthma in children under 5 years of age since there are no standardized pulmonary function tests for this age group. The presumptive diagnosis of asthma in infants and preschoolers is mainly based on clinical characteristics, the presence of recurrent and severe bronchial obstruction episodes, and the frequent presence and association of personal or family history of atopy.

In 2018, an article published in the *Lancet* redefines the concept of asthma, noting that this term should be used to describe a group of symptoms and signs that have different underlying pathophysiological mechanisms³. Thus, the objective of this study was to determine the hospitalization, lethality, and mortality rates in infants and preschoolers discharged with a diagnosis of asthma and acute bronchitis throughout our country.

Patients and Method

Prospective historical epidemiological and population-based study. This implies that clinical profiles were not analyzed because there is no individual information on each patient.

To have a fuller insight into bronchial obstructive pathology in children under 5 years of age, we decided to include in this study both children diagnosed with bronchial asthma and obstructive bronchitis. The term obstructive bronchitis is a local term, not used anywhere else in the world and therefore does not exist in the ICD-10 codes. Thus, other codes were used that implicitly involve the presence of bronchial obstruction such as acute bronchitis due to Respiratory Syncytial Virus or acute bronchitis due to *Mycoplasma Pneumoniae*. In this study, the terms acute bronchitis and obstructive bronchitis were considered equivalents.

We studied the evolution of the overall and regional hospitalization rate of acute bronchitis and asthma in children under 5 years of age from the years 2002 to

2017 and calculated the overall mortality rate for both pathologies. To obtain the hospitalization rates, data were extracted from hospital discharge records provided by the Department of Statistics and Health Information (DEIS) of the Chilean Ministry of Health⁴.

Information corresponding to ICD10 codes for asthma (J450, J451, J458, J459, and J46X) and acute bronchitis (J20.0, J20.4, J20.5, J20.6, J20.8, J20.9, and J22) was selected. Variables available in this database such as age (years), sex, duration of hospital stay, hospitalization date, and discharge condition were included. Patients diagnosed with bronchiolitis were excluded because it is a disease with a different pathophysiology, that presents with necrosis of the respiratory epithelium and not a bronchoconstriction process itself. While it is true that some of these patients present obstructive signs, the parenchymal component is the most important, with the predominant presence of crackles on auscultation.

The sizes of the populations at risk of hospitalization were obtained from population projections provided by the National Institute of Statistics (INE)⁵. The mortality rate was obtained by calculating the ratio between the number of deaths due to acute bronchitis and asthma in children under 5 years of age and the exposed population. Lethality was obtained by calculating the ratio between the number of deaths due to acute bronchitis and asthma and the number of patients affected by this condition.

The evolution of hospitalization rates was analyzed using a first-order linear autoregressive model (Prais-Winsten). Comparisons between age ranges and geographic regions were performed using Poisson regression analysis, in which the comparison measure was the incidence rate ratio (IRR). Continuous variables were described as mean and standard deviation, median and interquartile range (IQR), while qualitative variables were described as frequencies and proportions. Confidence intervals were established at the 95% level and 5% was considered significant. The data was processed in the STATA 14.0 statistical software.

Results

During the analyzed period, 2,823,064 hospital discharges were registered for all respiratory and non-respiratory causes in children under 5 years of age. 151,580 (5.4%) corresponded to acute bronchitis and asthma. In this age group, acute bronchitis was the discharge diagnosis in 141,811 cases (93.6%) and asthma in 9,769 (6.4%). The mean age of these children was 1.0 ± 1.3 years. 51.1% were younger than 1 year and 83.7% were younger than 2 years. Patients diagnosed with acute bronchitis had a mean age of 1.9 ± 1.4 years

while those diagnosed with asthma had a mean age of 2.1 ± 1.4 years. This difference was statistically significant ($p < 0.0001$).

Of the patients hospitalized with a diagnosis of asthma, 5,404 (55.3%) were male and 3,762 (44.7%) were female, and in those diagnosed with acute bronchitis, 78,479 (55.3%) were male and 54,741 (44.7%) were female. This difference was not statistically significant ($p = 0.93$).

The mean duration of hospital stay was 3.8 ± 2.9 days, with no significant differences by sex or type of diagnosis. A negative correlation was observed between age and length of stay in children diagnosed with acute bronchitis (Spearman Correlation - 0.11 $p < 0.0001$). In contrast, there was no association between age and length of stay in children diagnosed with asthma (Correl Spearman - 0.01 $p = 0.40$). During the analyzed period, there was no variation in the median length of stay, which was 3 (IQR 0), regardless of diagnosis. A clear seasonality was observed in hospitalizations due to acute bronchitis, with a significant increase in July (Figure 1). This seasonality was not observed in patients diagnosed with asthma.

When analyzing the evolution of hospitalization rates according to diagnosis, it was observed that the hospitalization rate due to acute bronchitis decreased from 79.7 to 56.1 per 10,000 inhabitants at a rate of 1.49 hospitalizations per 10,000 inhabitants per year ($p < 0.0001$). In contrast, the hospitalization rate due to asthma increased from 2.4 to 7.6 per 10,000 inhabitants at a rate of 0.3 hospitalizations per 10,000 inhabitants per year ($p < 0.0001$) (Figure 2; Table 1). When analyzing hospitalization rates by age, it was observed that the reduction in the overall hospitalization rate due to acute bronchitis was mainly caused by a signi-

ficant decrease of this rate in children under 1 year of age (Table 2 and Figure 3). The hospitalization rates in the other age groups remained constant over time (Figure 3). The increase in the overall hospitalization rate due to asthma was caused by a significant increase in hospitalization rates observed in all age groups for this disease, especially in children older than 4 years (Table 3 and Figure 4).

When evaluating the mean hospitalization rate due to asthma in children under 5 years of age by region, it was observed that the Tarapacá Region had the highest mean rate and that the Atacama Region had the lowest one (Table 4). On the other hand, the Los Ríos Region had the highest mean hospitalization rate due to acute bronchitis, and the Arica y Parinacota Region had the lowest one (Table 4).

During the studied period, 101 children died, representing a lethality of 0.07%. All the deceased patients were diagnosed with acute bronchitis and 87.1% of them were children under 2 years of age. The mortality rate during the studied period was 0.52 per 100,000 inhabitants among patients with acute bronchitis, and no mortality was found in children diagnosed with asthma.

Discussion

In this study, the epidemiology of hospitalizations due to obstructive bronchial pathology in children under 5 years of age was described for the first time. Most of the patients hospitalized had a diagnosis of acute bronchitis (93.6%), were under 2 years of age, were male, and were hospitalized during the winter months, especially in July. This coincides with the

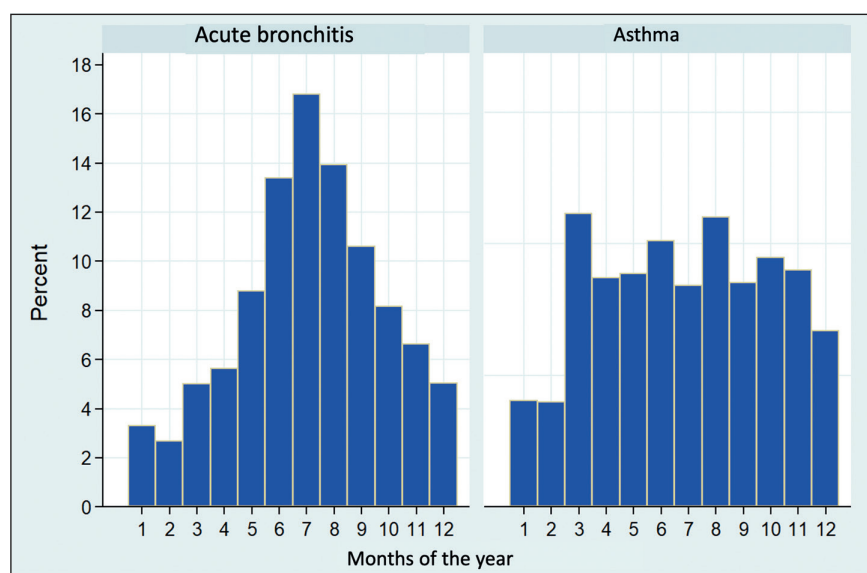


Figure 1. Seasonality of hospitalizations due to acute bronchitis and asthma.

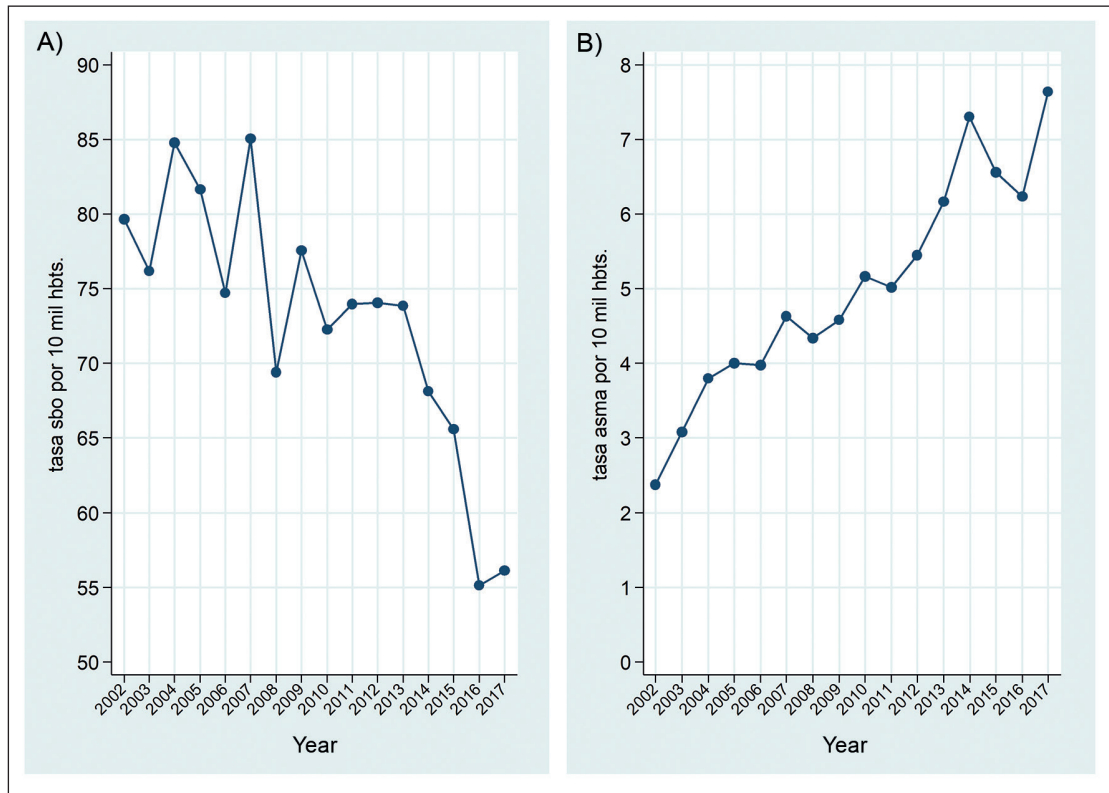


Figure 2. Hospitalization rates per 10.000 inhabitants. **A)** Acute bronchitis **B)** Asthma.

Table 1. Hospitalization rates per 10.000 inhabitants in children under 5 years of age with acute bronchitis and asthma

Year	Acute bronchitis	Asthma	Acute bronchitis and asthma
2002	79.7	2.4	82.0
2003	76.2	3.1	79.3
2004	84.8	3.8	88.6
2005	81.6	4.0	85.6
2006	74.7	4.0	78.7
2007	85.0	4.6	89.7
2008	69.4	4.3	73.8
2009	77.6	4.6	82.1
2010	72.3	5.2	77.4
2011	74.0	5.0	79.0
2012	74.1	5.5	79.5
2013	73.8	6.2	80.0
2014	68.1	7.3	75.4
2015	65.6	6.6	72.2
2016	55.1	6.2	61.4
2017	56.1	7.6	63.8

annual increase of viral infections in our country, in which Respiratory Syncytial Virus and Influenza Virus are predominant^{6,7}.

The epidemiological profile of children diagnosed with asthma was like that of children diagnosed with acute bronchitis, with the difference that hospitalizations did not show a seasonal pattern. This contrasts with the increase of hospitalizations observed in autumn and spring in asthmatic patients older than 5 years¹. This could be explained by the fact that in this study, the total number of asthmatic patients was only 9,769 and, in the study conducted on asthmatic patients older than 5 years, the number of patients hospitalized due to asthma was 23,382¹. This numerical difference may have meant that there were not enough patients to show a trend in terms of seasonality.

The hospitalization rate due to asthma in children under 5 years of age was 7.6 per 10,000 inhabitants in 2017, very similar to the rate in those older than 5 years in our country, which was 7.8 per 10,000 inhabitants in 2014¹. The hospitalization rate in children under 5 years of age was observed to be like the one reported by Spain in this age group, 5.7 per 10,000 inhabitants⁸. However, in the United States, the hospitalization rate due to asthma in children under 5 years of age was 51.2 per 10,000 inhabitants in 2009, almost 7 times higher

Table 2. Evolution of h hospitalization rate in children with acute bronchitis by age and by year

Year	Rate in children < 1 year old	Rate in children 1 year old	Rate in children 2 year old	Rate in children 3 year old	Rate in children 4 year old
2002	240.9	83.8	38.9	26.1	17.4
2003	216.5	79.4	45.8	27.2	20.6
2004	245.4	85.7	47.5	33.8	21.1
2005	241.8	79.8	44.3	29.1	21.2
2006	215.5	76.3	40.6	27.0	18.7
2007	242.9	85.8	42.6	30.4	22.7
2008	227.3	81.9	59.8	26.6	16.7
2009	210.6	81.7	43.3	24.6	18.5
2011	196.0	77.9	45.9	28.1	18.7
2012	192.5	85.2	47.6	29.6	16.8
2013	186.3	86.6	48.1	31.4	20.0
2014	155.0	91.5	44.1	31.5	20.3
2015	150.2	85.2	42.8	29.4	20.1
2016	133.3	68.5	34.4	22.7	15.5
2017	129.0	74.8	37.8	23.3	15.1
slope	-8.23	-0.26	-0.28	-0.17	-0.22
p-value	0.0000	0.5560	0.4550	0.4960	0.0790

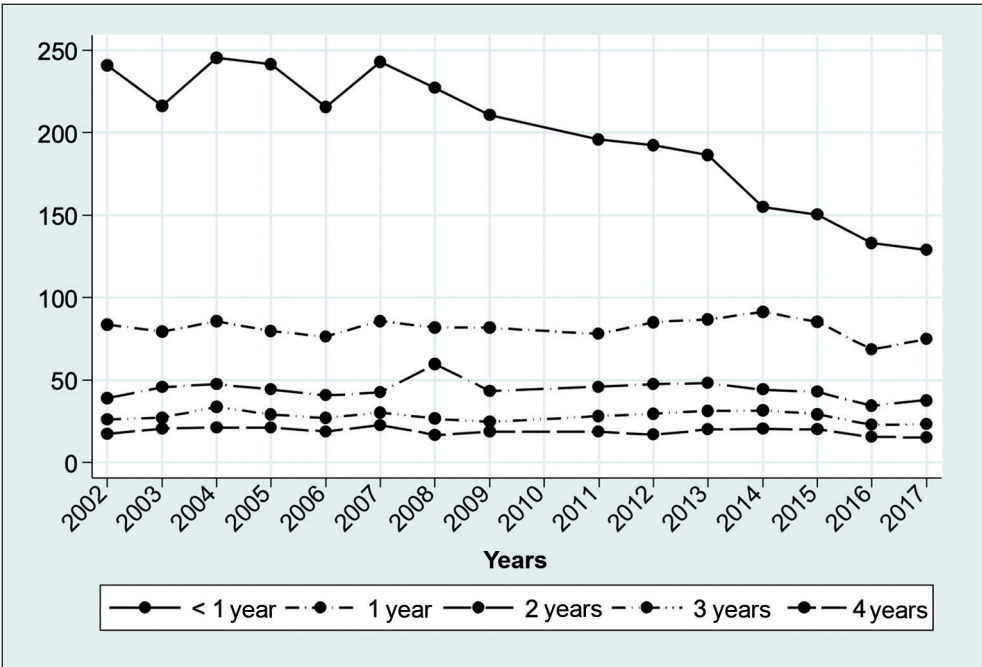


Figure 3. Evolution over time of hospitalization rates due to acute bronchitis by age

Table 3. Evolution of the hospitalization rate in children with asthma by age and by year

Year	Rate in children < 1 year old	Rate in children 1 year old	Rate in children 2 year old	Rate in children 3 year old	Rate in children 4 year old
2002	0.9	0.8	1.9	3.3	4.8
2003	1.1	0.9	2.4	4.5	6.2
2004	3.1	1.6	2.8	4.6	6.7
2005	1.4	1.5	2.7	4.9	9.2
2006	2.1	1.6	2.7	5.2	8.0
2007	2.0	2.0	3.9	6.6	8.6
2008	3.0	0.1	4.2	6.2	8.2
2009	1.6	1.8	3.7	6.2	10.0
2011	1.2	2.0	4.7	7.7	9.9
2012	1.7	2.0	4.3	8.9	10.4
2013	2.7	3.2	5.0	8.5	11.2
2014	2.3	4.8	5.1	9.9	14.2
2015	2.5	5.0	5.1	7.9	12.3
2016	2.9	4.6	5.3	7.5	10.9
2017	4.3	6.2	6.4	8.9	12.4
slope	0.10	0.32	0.25	0.36	0.47
p-value	0.0190	0.0000	0.0000	0.0000	0.0000

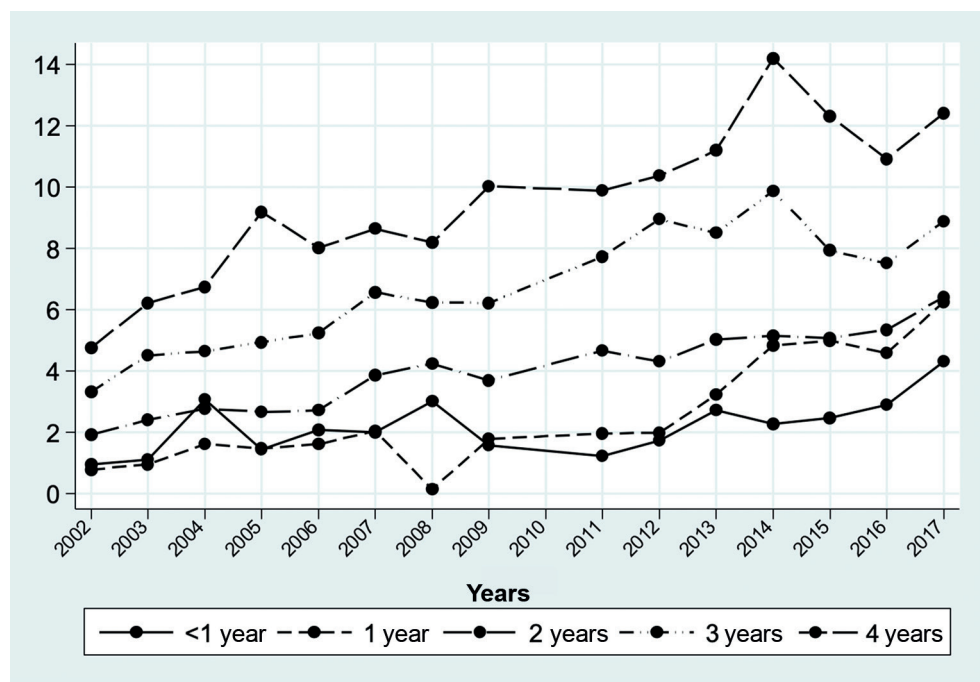


Figure 4. Evolution over time of hospitalization rates due to asthma by age.

Table 4. Mean hospitalization rate per 10.000 inhabitants in children under 5 years of age with acute bronchitis (AB) and asthma

Region	Asthma	AB	BA + Asthma
Tarapacá	7.45	17.25	24.7
Antofagasta	3.35	32.25	35.55
Atacama	1.05	31.95	33
Coquimbo	3.2	24.6	27.75
Valparaíso	4.85	70.65	75.5
O'Higgins	3.6	45.7	49.3
El Maule	1.3	107.55	108.85
El Bio Bio	5.35	97.8	103.15
La Araucanía	4.25	102.8	107.05
Los Lagos	9.2	57.3	66.5
Aysén	5.85	86.15	91.95
Magallanes y Antártica chilena	1.2	30.15	31.35
RM de Santiago	7.9	56.2	64.15
Los Ríos	3.75	153.8	157.55
Arica y Parinacota	1.65	5.05	6.7

than that found in this study and almost 9 times higher than the one reported in Spain⁹. These differences could be reflecting regional variations, which may be of multifactorial origins such as genetics, perinatal exposure, diet, obesity, exposure to cigarette smoke, and indoor and outdoor air pollutants¹⁰.

Another possible explanation for this significant difference could be an underdiagnosis of asthma in Chile and Spain or an overdiagnosis of the disease in the United States, and differences in the diagnostic criteria for asthma in children under 5 years of age in the mentioned countries. Underdiagnosis usually occurs because the healthcare team has lack of awareness of the disease, and overdiagnosis occurs because clinical suspicion is not confirmed with pulmonary function tests¹¹.

The diagnosis of bronchial asthma should be suspected in any patient presenting with repeated episodes of bronchial obstruction, considering that in between these episodes the patient may be completely asymptomatic or have some symptoms such as coughing induced by exercise, laughter, or crying. The diagnostic hypothesis should always be confirmed with pulmonary function tests that prove variable airflow obstruction and/or a positive response to the bronchodilator¹².

Clinically, the diagnosis of asthma in children under 5 years of age is very difficult, in addition, there is a lack of standardized pulmonary function tests for this age group. To classify an infant or preschooler as

asthmatic based solely on clinical findings is very complicated since obstructive bronchial pathology is very frequent in this age group and is in most of the time secondary to frequent viral or bacterial infections, not to the diagnosis of asthma¹³. These episodes tend to be very recurrent and are usually related to the beginning of daycare in infants or kindergarten in preschoolers. These episodes usually diminish over time, as the child grows older, and they usually disappear before the age of 6¹⁴.

This was demonstrated in the Tucson Cohort where 1,246 children were followed from the newborn period to school age. 48.5% of these children wheezed at some time during follow-up. The children who wheezed were grouped according to common clinical characteristics, and 3 phenotypes could be established: transient wheeze, persistent non-atopic wheeze, and persistent atopic wheeze. The first group started wheezing during the first months of life, showing an increase up to the age of 3, but stopped wheezing completely before the age of 6. The second group began wheezing around the age of 3, many continued wheezing at the age of 6, but then stopped wheezing at age 11. Finally, the third group began wheezing in the first months of life and continued wheezing into adulthood. Only this last subgroup of patients corresponded to the truly asthmatic patients¹⁴.

Recurrent wheezing in preschoolers is a highly prevalent problem, with 50% of all children having at least

1 episode of wheezing in the first 6 years of life; however, only 4.4% of children under 4 years of age have a diagnosis of asthma¹⁵. Although it is estimated that 80% of children with asthma present symptoms at a very young age, this is an infrequent diagnosis within the large group of children with recurrent wheezing under 5 years of age¹⁶.

In school-age children with a suspected diagnosis of asthma, lung function tests such as spirometry are requested. If this test is normal, the study should be complemented with bronchial provocation tests such as the methacholine test or exercise test¹². These tests require the patient's cooperation, so they are generally performed in children over 5 years of age, for whom reference values are standardized. However, in specialized centers, spirometry could be performed on preschoolers¹⁷.

There are pulmonary function tests that are effort independent, so they would be useful in preschoolers. Impulse oscillometry, for example, is promising in this age group since it is performed during tidal breathing¹⁸. Hopefully, soon, we will have biomarkers that will help us to establish a more accurate diagnosis of asthma in this group of patients.

Regarding acute bronchitis, it was observed that the hospitalization rate in children under 5 years of age was 7 times higher than the hospitalization rate in children with asthma. We did not find data in the literature on hospitalization rates due to acute bronchitis in children under 5 years of age to compare our results. The hospitalization rate due to acute bronchitis observed in this study was very similar to the hospitalization rate due to asthma in children under 5 years of age in the United States (USA). Regarding this observation, one may wonder if the diagnosis of asthma in hospitalized patients in this age group in the USA corresponds really to asthma or if it is perhaps just a wheezing child, known as acute bronchitis in our country.

The high rate of hospitalization due to acute bronchitis could be explained by the high frequency of exposure to viral infections in young children, the main trigger of bronchial obstruction. The literature is consistent in demonstrating that most acute lower respiratory tract infections (LRTI) in children under 5 years of age and especially in children under 2 years of age are mainly caused by viruses. In a study carried out in Turkey in 422 children hospitalized due to acute LRTI, 73.7% of the cases presented viral etiology, with Respiratory Syncytial Virus (RSV) in 33.1% and Rhinovirus (RV) in 32.7%¹⁹.

In this study, 78.6% of the hospitalized children were under 5 years of age and 56.1% were under 1 year of age¹⁹. Similar figures were observed in two prospective publications from Australia and Bulgaria^{20,21}. In a one-year retrospective observational study conducted

in a pediatric hospital in Santiago, it was observed that 74.4% of 1,856 hospital admissions due to acute LRTI, corresponded to children under 2 years of age²². The etiology was viral in 80.5% of cases, with RSV being the most frequently isolated virus in 57.9%, followed by Metapneumovirus in 11.8%, and Influenza Virus in 10.2%²².

Young children are at a higher risk of suffering respiratory infections because they are highly exposed to viruses and at the same time their immune system is still immature. Humoral and cellular immunity does not fully mature until the fifth or sixth year of life. Infants have immature cellular immune system function and activation, with an imbalance toward Th2-type cytokine production. All this reflects a transient immaturity of a developing immune system, which makes these children more susceptible to respiratory tract infections compared with older children²³.

The most relevant finding of this study is the demonstration of a significant decrease in the hospitalization rate due to acute bronchitis in children under 5 years of age from 79.7 out of a population of 10,000 in the year 2002 to 55.1 per 10,000 in the year 2017. This decrease is mainly due to the group of children under 1 year of age. The reduction in the hospitalization rate is probably related to several factors such as the implementation of abbreviated hospitalization wards in primary care centers, the additional allocation of resources in the winter months to increase the number of medical and physiotherapy hours, increased availability of drugs and supplies, the creation of an additional network of beds, and social communication efforts that are part of the winter campaign established by the Ministry of Health every year since 1994^{24,25}.

Interestingly, when analyzing the evolution of hospitalization rates by discharge diagnosis, it was observed that the hospitalization rate due to acute bronchitis showed a reduction over time, while that due to asthma showed an increase. This could indicate different underlying pathophysiological mechanisms in both diseases, which manifest themselves in very similar symptoms. The increase in hospitalization rates due to asthma in children under 5 years of age coincides with the increase in hospitalization rates in asthmatic patients older than 5 years observed in another study¹.

Significant regional variations in hospitalization rates were observed in both acute bronchitis and asthma. These differences are probably of multifactorial origin, with factors associated with the host and others with environmental factors¹⁰. Other publications have established as important risk factors day care attendance and low level of maternal education^{26,27}. Also, the importance of climatic factors in the rate of hospitalization has also been demonstrated, which could explain the low hospitalization rate due to acute bronchitis in

the Arica and Parinacota Region (warm climate) and the high rate in the Los Ríos Region (cold and humid climate). In a study conducted in China, it was observed that the hospitalization rate was significantly correlated with climatic factors such as temperature, atmospheric pressure, amount of rainfall, and relative air humidity. It was found that the lower the temperature, the higher the number of hospitalizations²⁸.

Environmental pollution plays an important role as demonstrated by a study carried out in Vietnam and another in China which showed a positive association between high levels of different pollutants such as particulate matter PM10, PM 2.5, SO₂, NO₂, and the number of hospitalizations due to acute lower airway respiratory diseases and asthma^{29,30}. A significant association has also been demonstrated with indoor pollutants, especially the use of biomass fuels^{31,32}. This is very common in homes in the south of our country where firewood is routinely used for both cooking and heating.

In this study, there was no asthma mortality in children under 5 years of age, which contrasts with the 0.37 per 100,000 inhabitants found in those older than 5². This could be explained by the lower number of patients under 5 years of age diagnosed with asthma or by a lower severity of the disease in this age group. The mortality rate reported by Brazil is 0.53 per 100,000 inhabitants and in the United States 0.18 per 100,000 inhabitants^{33,34}. The mortality rate of acute bronchitis was 0.52 per 100,000 inhabitants, with most of the deceased patients being under 2 years of age. We did not find in the literature data on the mortality rate due to acute bronchitis in children under 5 years of age to compare our results. The differences found in mortality according to the discharge diagnosis could again be explained by different underlying pathophysiological mechanisms between the two entities or by the lower number of patients discharged with a diagnosis of asthma compared with acute bronchitis.

The main strength of this study is that it reports for the first time the hospitalization and mortality rates due to acute bronchitis and asthma in children under 5 years of age, thus complementing the epidemiological data already known for children over 5 years of

age in our country. The main weakness, on the other hand, is the quality of the available records, since we do not have detailed data on hospitalizations, such as severity, presence of comorbidities, use of maintenance treatment, or type of therapy received by each patient during the hospitalization. In addition, there could be a bias at the time of establishing the discharge diagnosis since there are no clear guidelines to define whether the cause of hospitalization in this age group corresponds to asthma or acute bronchitis. Despite this, we believe that the results of this study are a starting point to better understand the epidemiological situation of obstructive bronchial pathology in children under 5 years of age in our country.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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