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ORIGINAL ARTICLE

Direct costs of low respiratory infection due to RSV in children under one year

Costos directos de infección respiratoria baja por VRS en menores de un año

Juan Zepeda T.[a], Jorge Vásquez Z.[a], Luis Delpiano M.[b]

[a]Program of Specialization in Pediatrics, University of Chile
[b]San Borja Arriarán Clinical Hospital, Santiago, Chile

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Abstract

Introduction: Considering the high prevalence of respiratory infections in hospitalized infants with Respiratory Syncytial Virus (RSV), the objective of this study is to determine the direct costs of this infection. **Patients and Method:** Prospective longitudinal study in infants under one year of age hospitalized due to RSV during 2015. The patients were divided into 2 groups, Group 1 patients without risk factors and Group 2 patients with risk factors (prematurity, oxygen dependence, bronchopulmonary dysplasia, heart disease, immunocompromised patients), comparing each other variables such as nutritional status, gender, breastfeeding, discharge diagnosis, radiological diagnosis, length of hospital stay, among others. Direct costs for hospitalization were estimated according to the fees of the National Health Fund (FONASA) and the Modality of Institutional Care (MAI). **Results:** The total patients admitted in the period were 260: 234 (90%) in Group 1 and 26 (10%) in Group 2. The average hospital stay for Group 1 was 7.3 days (SD+5.1) with a median of 6 days, and 13.6 days (SD+16.3) for Group 2 with a median of 7 days ($p < 0.05$). The direct costs associated with RSV hospitalization were on average CLP $ 413,529 (US$ 632.1) for Group 1, and CLP $ 744,260 (US$ 1,137.6) for Group 2 ($p < 0.05$). There was also statistically significant higher cost for Group 2 due to tests and drugs ($p < 0.05$) and costs per day of hospital stay ($p < 0.05$). **Conclusion:** These values, known for the first time in the national reality, confirm the high cost of these infections and particularly in risk groups.

Keywords:
Respiratory Syncytial Virus;
costs;
bronchiolitis

Correspondence:
Dr. Juan Zepeda
juanzepedatoro@gmail.com

Introduction

The respiratory syncytial virus (RSV) is a common cause of respiratory infections in children, which also has a high impact in hospitalization and community morbidity[1-4]. It is the main cause of lower respiratory tract infections (LRTIs) in infants and preschoolers worldwide.

RSV clinical symptoms include a large manifestation spectrum, from acute upper respiratory infections to lower respiratory compromise, such as bronchitis and pneumonia. Worse evolution risk factors include premature infants, younger than six months and patients with comorbidities, among other, who would require a longer hospitalization[6-8], and a higher risk of severe complications, such as the need of mechanical ventilation or even death[9-12]. International studies show high expenses from families and from the health system associated with hospitalizations due to RSV infections in patients younger than one year [9-11].

Our objective is to determine said costs differentiated by known acute infection factors during one follow-up year since there is a lack of national data on health-related costs for LRTIs-RSV hospitalizations.

Patients and Methods

Design

Transversal prospective observational study in infants younger than one year hospitalized in San Borja Arriarán Clinical Hospital due to LRTI secondary to RSV during 2015. Inclusion criteria: children younger than 11 months and 29 days of age that were admitted in the Pediatric Unit and Intensive Care Unit (ICU) between May 1st and November 14th 2015 (17 to 45 epidemiological weeks), with a RSV infection diagnosis confirmed with the direct immunofluorescence method (DIF), performed in the Hospital central laboratory (Light Diagnostics™ Respiratory Panel 1 DFA, Merck-Millipore Laboratory), who were recruited after the execution of an informed consent.

Patients older than one year were excluded, without lower respiratory compromise, with viral coexistence (coinfection) diagnosis, positive bacterial cultures at admission, confirmed whooping cough, referred from or to another hospital center, and patients from the Neonatology service.

The sample size was calculated from the number of LRTI due to RSV hospitalizations in infants during the last four years, the average was 386 patients per year, therefore, the hospitalization probability for LRTI due to RSV is 1.5% (with a maximum of 3%) of the patients born in maternity as target population. A value of 250 subjects was obtained to estimate the direct health costs profile of hospitalized LRTI-RSV.

Variables to study

Age measured in months, gender, nutritional status, weight and height measured at the admission and according to the WHO nutrition guidelines, discharge clinical diagnosis, breastfeeding (Yes if breastfeeding lasted six months or more and No if breastfeeding never happened or was interrupted before six months), prematurity, bronchopulmonary dysplasia confirmed by a specialist physician at the discharge from neonatology, oxygen dependence, any patient admitted with O^2 requirements before the hospitalization, confirmed congenital heart disease, admission radiological diagnosis (performed by the treating physician based on local definitions), direct costs (valorization of all performed tests and received treatments), bed-days in the Basic or Intensive Care Unit, and average hospitalization days.

For the estimation of direct costs, a valorization was performed according to the Institutional Health Care Modality of FONASA (MAI) 2015 (Table 1) care costs, which are expressed in Chilean pesos (CLP $) and American dollars (US$) observed in the middle of the studied period (August 1st, 2015), where 1 (US$) is equal to CLP $671.11. Through a daily review of the patients and their clinical records, a spreadsheet of each service in order to translate it subsequently to monetary cost and cost per each hospitalization day.

Study groups

Group 1: infants with LRTI secondary to RSV, without comorbidities. Group 2: infants with LRTI secondary to RSV, with comorbidities considering the presence of prematurity, bronchopulmonary dysplasia (BPD), oxygen dependence, congenital heart disease, immunocompromised (primary immunodeficiency or AIDS-stage HIV).

Statistical analysis

Data was recollected in Excel spreadsheets. Central tendency and dispersion for quantitative type variables were calculated. For qualitative type variables, frequency tables and graphics were prepared. Chi-square test was used to compare the group dependent variable and the qualitative type variables of interest, and the T-Student test to compare independent sample medians and to compare dependent variables and qualitative variables related to costs, for tests, hospitalization days, and drugs. 95% confidence index and 5% error possibility (Value p = <0.05) were applied. SPSS analysis and Excel softwares.

Ethical aspects

Study approved by the Pediatric Research Committee of the University of Chile, Scientific Ethics Committee of the Central Metropolitan Health Service. An

Table 1. Cost - valuation of services according to FONASA 2015, Institutional Health Care Modality (MAI 2015)

Service	Unitary Cost (US $)	Service	Unitary Cost (US $)
Day bed basic	50,7	Blood culture	9,6
Day bed interval	101,8	Amonio	2,4
Day bed UCI	210,7	Lactic acid	4,2
Session of kinesioterapia	1,8	Lumbar puncture	10,7
X-rays thorax	21	EEG	17,5
Blood Complete count	3,4	Cerebral CT	72
C-reactive protein	7	Troponin	9,5
Respiratory Panel 1 DFA (RSV, human metapneumovirus, parainfluenza virus, rhinovirus, FLU virus,and adenovirus)	30	EKG	7,5
Direct immunofluorescence by Bordetella Pertussis	6,8	Echocardiography	42,7
Venous gases	4,2	B-C Hepatitis serology	16,7
Biochemical profile	9,6	VDRL	3,5
Magnesium	3,3	Elisa VIH	6,3
Plasmatic electrolytes	1,4	Abdominal ultrasound	29,2
Urine completes	6,3	Other ultrasound	20
Coagulation tests	1,6	Fecal Culture	7,8
bacteriological study	5	Rotavirus test	7,4
Blood group	2,7	Abdominal X-rays	10,4
Immunological profile (immunoglobulin)	19	Red Blood Cell Transfusion	28
Kinetic of the iron	6		

Table 2. Stratification of 260 infants hospitalized by LRTI for RSV of agreement to section etario and average of days of hospitalization

Section etario (Months)	Number of patients	Average of hospitalized days	Median of hospitalized days*
0-3	94	9.13	8
3^{+1} -6	51	8.47	6
6^{+1} -9	72	6.42	5
9^{+1} - 12	43	7.46	8

*Between group 0-3^{+1} months and group 6^{+1} -9 months: $p < 0,05$.

informed consent signed by one parent of each patient was obtained.

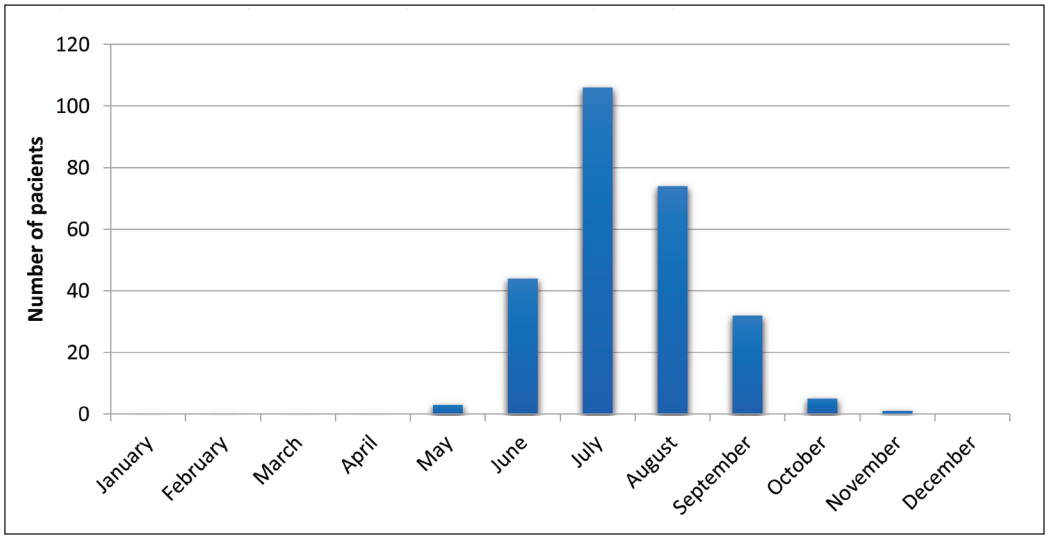
Results

260 infants younger than one year were admitted. Table 2 and 3 show the stratification and demographic characteristics. The average of hospitalization days was eight days for the total of patients (range 1 to 79 days), with a median of eight days. The bed occupancy index was 0.492.

Graphic 1 shows the distribution of hospitalized patients, according to the month. Between June and August 2015, 87.1% of patients were admitted, being July the month with the higher number of admissions (40.3%).

According to demographic characteristics (Table 3), 91.1% of the patients were discharged with bronchiolitis or interstitial pneumonia diagnosis. It had a predominantly mixed radiological pattern, with exclusive presence of alveolar condensation of 8.8% in infants.

Per three-month age group (Table 2), the 0 to 3



Graphic 1. Distribution of 260 nursing babies with LRTI due to RSV, according to hospitalization month. HCS-BA, May to November, 2015.

months group had the higher number of hospitalized patients and the higher number of hospitalization days.

According to the nutritional assessment, infants with nutritional disorders by deficiency showed higher expenses in comparison to patients with nutritional disorders by excess and up to a 55% of the average expenses of all hospitalized patients (Table 4).

The total cost was CLP $ 115.969.769 (172,803 US$) with an individual average of CLP $ 446,141 (US$ 664.8), and a CLP $ 323,017 (481.3 US$) median. The age group younger than six months spent a 62.3% of the total, equivalent to CLP $ 72,275,577(107695.7 US$).

Every patient stayed in a basic bed at some moment of his or her hospitalization. 93 infants stayed in the Intermediate Unit (average of 4.5 hospitalization days) and 13 in the PICU (average of 6.2 hospitalization days). Out of the 2,079 bed-days, 1,572 were basic beds (CLP $53,055,600), 426 intermediate (CLP $ 29,091,540) and 81 PICU bed (CLP $ 11,454,210). The total cost of bed-days was $93,601,350 (139474.5 US$), which represents the 80.7% of the total cost.

Table 5 shows direct expenses of different items per infant with expected costs.

For each pre-established study group, 234 infants were included in the group 1 and 26 infants (10%) in the group 2. By comparing the hospitalization days between both groups, with a median of six days for both, group 2 showed an average of 13.6 hospitalization days and group 1 showed an average of 7.3 with a $p < 0.05$ value. Furthermore, the average cost of the group 1 was CLP $413,529 (US$ 616) and the group 2 was CLP $744,260 (US$1,109) with $p < 0.05$ (Table 6). There was a significant difference when comparing the average cost of tests and drugs between group 1 and 2. The patient with the lowest expense for hospitalization

Table 3. Demographic characteristics of 260 infants hospitalized by LRTI for RSV, may to november 2015

Variables	n	(%)
Gender		
Male	158	(60.8)
Female	102	(39.2)
Age (months)		
0 - 3	94	(36.1)
3^{+1} - 6	51	(19.7)
6^{+1} - 9	72	(27.7)
9^{+1} -12	43	(16.5)
Nutritional status		
Undernourished	8	(3.1)
Low weight	24	(9.3)
Normal weight	181	(69.5)
Overweight	34	(13.1)
Obesity	13	(5.0)
Radiological diagnosis		
Interstitial Pneumonia	70	(26.9)
Atelectasia	6	(2.3)
Consolidation intra-alveolar	23	(8.8)
Mixed*	161	(61.9)
Discharge diagnosis		
Bronchiolitis	145	(55.8)
Interstitial Pneumonia	92	(35.4)
Pneumonia (Consolidation intra-alveolar)	23	(8.8)
Comorbidities		
Oxygen dependence	2	(0.80)
No breastfeeding	29	(11.2)
Prematurity	24	(9.2)
CHD	4	(1.5)
Uso Surfactante RN	1	(0.4)
NRDS	6	(2.3)
BPD	3	(1.2)

*Mixed: include interstitial pneumonia, consolidation alveolar and hiperinflate lungs.

Table 4. Total cost by nutritional state. HCSBA 2015

Nutritional status	Number of patients	Cost (US$)	Average (US$)
Overweight-Obesity	48	23,967	499
Normal weight	181	117,058	647
Undernourished-Low weight	32	31,818	994
Total	260	172,843	665

Table 5. Costs for nursing babies by item. HCSBA 2015

	n	Minimum (US$)	Maximum (US$)	Median (US$)
Costs for exams and medication	260	35	734	152
Costs for hospitalization day	260	51	4,900	537
Total cost	260	117	5,299	665

Table 6. Comparison of hospitalization day and direct costs in LRTI secondary to RSV between group 1 and 2

	Group	N	Average	Value p
Total hospitalization days	Group 1	234	7,378	0.00
	Group 2	26	13,615	
Costs for exams and medication	Group 1	234	US$ 146	0.03
	Group 2	26	US$ 208	
Costs for hospitalization days	Group 1	234	US$ 489	0.00
	Group 2	26	US$ 978	
Total cost	Group 1	234	US$ 616	0.00
	Group 2	26	US$ 1,109	

belonged to the group 1 with a value of CLP$ 78,590 (US$117) and the highest hospitalization cost belonged to the group 2, reaching a cost of CLP$ 3,556,151 (US$5299). After discharging both extreme values, for 258 patients the average global cost was CLP$ 435,512 (US$649) per patient.

In the group 2, the risk factors that were associated with higher costs were the history of MV during birth, BPD, and oxygen dependence. After establishing the relation of costs between the average of the different variables with respect to the total average of studied patients, the patients from group 2 have higher costs than the average. Finding that patients with history of neonatal respiratory distress syndrome (NRDS), or those who need MV at birth increase the expenses more than three times in relation with the average when they were admitted for LRTI secondary to RSV. Likewise, patients with history of BPD and oxygen dependence increase the cost 4.3 times more than the general average. Other relevant information is that those patients who did not receive breastfeeding or breastfeeding was removed before six months old showed expenses 1.5 higher than in average studied patients (Table 7).

The variables: gender, nutritional status, discharge diagnosis, and radiological diagnosis compared in both groups did not show any statistical significance in relation to the total cost of hospitalized patients. After analyzing the t-Student test for tests and drugs cost, hospitalization days, total cost, and total hospitalization days between group 1 and 2, it was found a statistical difference by associating group 2 with patients with comorbidities that have higher costs than group 1.

There were seven premature infants that received Palivizumab® (record of the pediatric bronchopulmonary center). None of them were hospitalized during the studied period. There were no deaths in this infant group.

Table 7. Cost relation with demographic variables (nutritional state, sex, age, gestational age) and variation by average

	Patients (n)	Total costs (US$)	Average for pacient by category (US$)	Average % variation costs
Total patients	260	172,871	664	
Overweitght and obesity	48	29,971	499	75%
Normal weight	180	117,077	650	97.8%
Low weight and Undernourished	32	31,823	994	149.5%
Men	158	109,229	691	103.9%
Women	102	83,641	623	93.8%
< than 6 months	145	107,713	742	111.7%
> than 6 months	115	65,158	566	37.5%
NB term	233	144,480	620	93.2%
Prematurity	24	26,625	1,109	37.5%
NRSD	6	12,115	2,019	303%
MV for new borns	4	10,478	2,619	394%
BPD	3	8,632	288	432%
O2 requirements	2	5,850	2,925	439%
CHD	4	2,734	921	138%
No breastfeeding	29	29,560	1,019	153.3%

BPD: Bronchopulmonary dysplasia. MV: Mechanical Ventilation. NB: New Born. NRSD: Neonatal Respiratory Distress Syndrome. CHD: Congenital Heart Disease.

Discussion

This is the first study in our country that allows knowing direct costs associated to LRTI secondary to RSV in hospitalized infants younger than one year in the public service, and also differentiating costs of each patient with or without comorbidities.

Most of the infants were hospitalized from June to August 2015, according to other publications and with the epidemiological vigilance curve form the Public Health Institute[13]. According to the "Winter 2015 Campaign Compliance Report" from the Scientific Ethics Committee of the Central Metropolitan Health Service, which belongs to the San Borja Arriarán Clinical Hospital and the El Carmen de Maipú Hospital. 3,705 pediatric patients were hospitalized, 1,636 patients (43%) were due to respiratory causes, therefore, hospitalized infants younger than one year in the San Borja Arriarán Clinical Hospital due to RSV represent 16% of the total of hospitalizations due to respiratory causes in 2015, which indicates the respiratory pathology's hospitalization high cost.

It emphasizes a higher incidence in males, a higher hospitalization proportion of infants younger than six months (55.8%) and with bronchiolitis or interstitial pneumonia diagnosis (91.2%), with a lower pneumonia percentage (8.8%). Many studies identify risk factors related to the evolution of children with respiratory virus infections and, in the particular case of RSV, it include premature infants, younger than six months and patients with comorbidities due to a history of a longer stay in the hospital. While cardiac patients, patients with chronic pulmonary diseases and immunosuppressed have an increased risk of complications, such as the need for mechanical ventilation, stay in intensive care units, and even death[14-17]. The test and drugs, hospitalization days, total cost and total days of hospitalization cost variables between group 1 and 2 showed a statistical significance after associating group 2 of patients with risk factors to a higher direct cost, which can be prevented with prevention activated aimed to those infants.

When comparing both study groups, group 2 showed an average number of hospitalization days with a statistically significance value ($p<0.05$), being this item the most expensive one among considered costs. However, it was different considering gender, nutritional status, discharge diagnosis, and radiological diagnosis variables when comparing both groups. In the studied population, other variables were identified, such as the malnutrition, breastfeeding during a period shorter than six months, neonatal respiratory distress syndrome and the use of mechanical ventilation at birth, as variables, which were associated to a

higher average cost, and therefore, indicators of more complications in their evolution.

In this study, we demonstrate a higher cost for the patient group that we defined as a group at higher risk. Direct costs derived from bed-days, tests, and drugs.

It seems to be effective to extend and aim complementary preventive activities to prophylaxis with monoclonal antibodies in premature patients and other members of the risk factor groups. Our findings indicate the prolonged breastfeeding phenomenon and the nutritional recovery are immediate actions. Aimed vaccination strategies for RSV in risk groups or antenatal actions must be certainly evaluated in the future.

In the USA, the RSV is responsible for annual costs that vary from 365 to 565 million of dollars[7,24]. In this study, the total cost was CLP$ 115,969,769 (177,300 US$) in the 260 patients with an average cost of CLP$ 446,141 (682 US$). It is not possible to compare both countries, mainly due to the different demographic data and since our study has a limited set of cases and the study was only performed in one Hospital in Santiago, Chile. However, we can mention that studies in Ehlken[9], Germany, 2005 determined that the average cost for hospitalized patients younger than 36 months due to RSV is EUR 2,722 (CLP$2,027,754). This is quite higher than our average per patients, and since the evaluation was performed by Leader[11] in hospitalized patients younger than one year, in the USA, due to RSV determined that the average cost was US$ 214.4 for a term newborn and US$ 643.6 for premature newborns. It is lower than our costs and very different from what McLaurin[14]reported in 2016, also focused on infants hospitalized due to RSV, with a cost of US$ 10,570 for term newborn, US$ 19,931 for premature newborns of 33 to 34 weeks and US$ 40,813 for premature newborns younger than 29 weeks.

Our study does not include as a variable the consignment of the history of previous LRTI or current viral co-infection. Recent studies suggest that previous LRTI secondary to rhinovirus and coronavirus have been associated with asthma development in the preschooler period[19-22], and other reports have indicated that viral co-infection, such as parainfluenza virus/RSV and metapneumovirus/RSV are also associated with asthma development in later stages[18-23], which contributes to higher costs due to future expenses related to this respiratory morbidity. Regarding the severity and viral co-infection, in the Martínez study, it was not possible to demonstrate that the presence of viral co-infection had a relation with a more severe clinical evolution [25].

The LRTI diagnosis with DIF has a sensitivity, which ranges from 70% to 90% in ideal conditions during the epidemic season and a specificity higher than 90% in periods of high community prevalence. The RSV detection can be improved with molecular biology as a polymerase chain reaction (PCR), a more sensitive method that can increase the screening rate for other LRTI producer agents, and to increase the viral co-infection diagnosis. In a national study, which included 110 patients younger than 18 years by PCR technique, determined a 37% of viral co-infection, confirming its frequency in pediatrics, even in older ages than those in our study[14,25]. The use of PCR or another improved molecular biology technique, although, it allows to increase the sensitivity to diagnose infections, co-infections and eventually, to search for associations with higher severity and extension of hospitalizations[27], it also has a cost disadvantage and it is not universally available. Our hospital had the viral identification through immunofluorescence during the studied period[26].

Probably the costs are undervalued since other direct and indirect costs were excluded from the perspective of the payer and the patients. For example, those associated to the transportation of caregivers of the hospitalized child, food costs during their visits, cost of medical leaves, and the loss of workdays, which indicate that the real value as social and statewide cost of this disease is much higher. Patients with infection due to RSV secondary to the stay in the hospital were not included, which is an event that increases costs greatly.

Knowing, on one side, that the co-payment from the FONASA C group corresponds to 10% of the institutional service and 20% for those in group D; and on the other hand, the co-payment for the families of hospitalized patients due to SRV in the group C was $25,503 and group D was $50,090, it can be deduced that the cost for patients from FONASA C is between the 7% and 10% of the family income and for the FONASA D group corresponds to 13.7% of the family income.

Direct costs obtained in this study from hospitalized infants due to LRTI secondary to RSV contribute valuable information for a further sanitary planning both intra-and extra-hospital in terms of prevention and management of epidemic crisis periods. This, but not limited to, should be the priority for those patients with known risk factors, which could be added to patients with early cessation from breastfeeding, with history of neonatal respiratory distress syndrome, and previous use of mechanical ventilation, which are factors that are probably associated to higher costs during the management of LRTI secondary to RSV .

The obtained information must also be considered when evaluating cost-efficiency studies in relation to the introduction of vaccines for this pathogen in the infant population. Lastly, there can be a lower variability in the management of these patients among the different hospital. The calculated data is only applicable at public health level, knowing that they can be even

higher in the private system. However, a study that considers other direct costs would determine more information in order to know the real cost of this viral infection in the group.

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: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

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

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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