

Cost of illness of RSV infection in a middle-income tropical country

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ABSTRACT

Background. Despite the burden of disease of Respiratory syncytial virus (RSV) infection in children, there are important gaps in knowledge about the potential impact in terms of health as well as social and healthcare resources. The aim of this study was to describe the economic burden of RSV in the first two years of life in Colombia.

Methods. We conducted a cost-of-illness study, taking a population prevalence-based approach. A decision tree model was constructed with a time horizon of two years. We defined the following outcomes: death, RSV infection with long term complications, RSV with acute complications, RSV without complications. Inpatient and outpatient costs were collected directly from medical invoices of patients who attended a tertiary referral hospital. Results. The mean cost per patient with an RSV infection was US\$ 178.35 CI 95% (30.7-541.67 US\$). The total cost of RSV infection in children less than 2 years in Colombia was US \$ 64 443 616 per year (CI 95% US\$11 092 902 – US\$195 722 867). In the probabilistic sensitivity analysis, the mean cost per patient with RSV infection was only sensitive to changes in the cost of recurrent wheezing, cost of outpatient visits and cost of hospitalizations.

Conclusion. The infection by RSV in Colombia generates a high economic burden on the health system. Generating comprehensive data on healthcare resource use and costs associated with RSV will help to provide valuable information for the development of cost-effectiveness models, and help guide prevention strategies against RSV.

Key words: cost, respiratory syncytial virus, Colombia.

Respiratory syncytial virus (RSV) is the most frequent cause of bronchiolitis worldwide.¹ In 2005, 33.¹ million episodes of RSV infections worldwide resulted in about 3.2 million hospital admissions, and 59,600 in-hospital deaths in children younger than five years.² Worldwide, RSV infection is the second cause of postnatal infant death after malaria, causing 137,000 deaths each year (equal to 6.7% of all newborn deaths).³

Despite the increased risk of RSV in children and the frequency of their complications, there is an

important gap in the knowledge concerning the potential impact in terms of health as well as social and healthcare resources. Most of the economic studies focused on assessing the efficiency of palivizumab for the prophylaxis of RSV infection and have not properly evaluated the impact of this infection beyond the acute episode phase.⁴⁻⁷ Many of these studies have been designed from the perspective of the payer and not from a social perspective, without including indirect costs such as those associated with job loss and family expenses. Likewise, no studies have evaluated the economic impact of such an infection in developing countries; in which the problem in terms of morbidity and mortality is growing.⁸ The aim of this study was to describe the economic burden of RSV infection in the first two years of life in Colombia.

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Material and Methods

Choice of model

We conducted a cost-of-illness study, taking a population prevalence-based approach. A decision tree model was constructed to estimate the cost of each episode of RSV infection (Fig. 1). The reason for using a decision tree to estimate the expected cost per patient is that this analytical approach reduces the possible selection bias in the population studied that over represents or underestimates both the frequency of the outcome and the derived costs. With this structure, the only factor that weighs the cost are the probabilities of the analytical model and not the chance that such events may or may not occur in the population secondary to selection bias.⁹⁻¹² The study protocol and their informed consent was reviewed and approved by the Institutional Review Board of Clinica Somer (No 281015) and the University of Antioquia (No 18/2015).

Target population

Children younger than two years of age admitted to the pediatric ward with a diagnosis of RSV infection were included in the study. Patients older than two years, without lower respiratory compromise, with positive bacterial

cultures on admission, confirmed whooping cough or those referred from another hospital center were excluded.

Setting and location

Rionegro is a city and municipality in Antioquia Department, Colombia, located in the subregion of Eastern Antioquia, at an average elevation of 2,125 meters above sea level. The average annual precipitation varies between 1,800 and 2,500 millimeters with an average temperature of 17 °C, with a peak in the presentation of RSV between March and April.¹³ The municipality of Rionegro has a total population of 101,046 inhabitants, the sixth largest populated area in Antioquia, with two tertiary referral hospital.¹⁴ Colombia's health system is composed by a social security sector and a private sector. The basis of the system is the General Social Security Health System, which has two plans, contributory and subsidized; all with a decentralized referral mechanism. The contributory regimen covers salaried workers, pensioners, and independent workers, with the subsidized plan covering anyone who cannot pay. The National Health Authority's functions under the system include an increase in the quality of health care and supervision, surveillance, and control of health insurance. Enrollment in the General Social

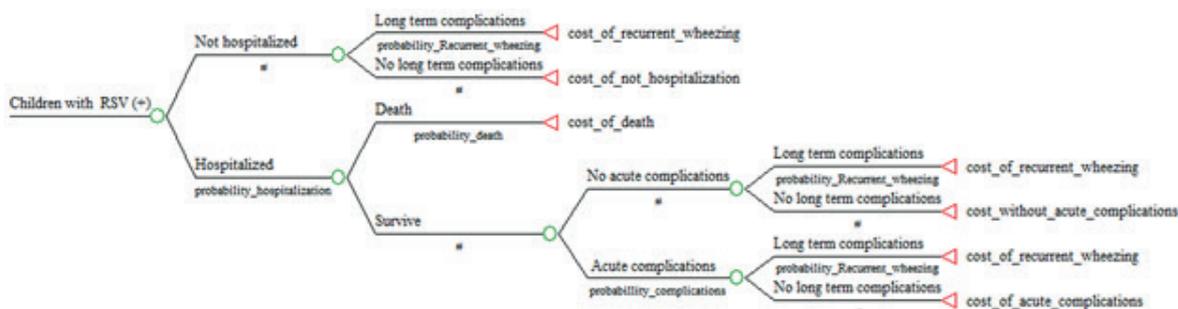


Fig. 1. Decision tree model.

- cRecurrent_Wheezing: cost of RSV patient with recurrent wheezing
- cNoHosp: cost of RSV patient Not hospitalized
- cWithoutComp: cost of RSV patient hospitalized without complications
- cComplications: cost of RSV patient hospitalized with complications
- cdeath: cost of RSV patient death
- pHosp: probability of hospitalization
- pCompl: probability of complications
- pdeath: probability of death
- pRecurrent Wheezing: probability of recurrent wheezing

Security Health System is obligatory and is handled through public or private health promotion agencies. Health care is provided by institutional health service providers. Those who can afford to purchase health insurance coverage on their own and who can pay for any uncovered fees out-of-pocket use the private sector.

Study perspective and Time horizon

We conducted a cost-of-illness study, taking a population prevalence-based approach. A decision tree model was constructed with a time horizon of two years. This analysis was performed from a societal perspective including direct and indirect costs. No discount rate was applied to the cost due to the short time horizon evaluated.

Choice of health outcomes

We defined the following outcomes according to the natural history of RSV infection: death, RSV infection with long term complications (recurrent wheezing), RSV infection only with acute complications, RSV infection without complications. In this model, the development of recurrent wheezing was assumed as the only long-term complication; since it is the most frequent respiratory complication in the first two years after the first infection.¹⁵ Among the acute complications included: pneumonia, atelectasis, sepsis, pleural effusions, and pneumothoraxes.¹⁶

Measurement and evaluation of probabilities of model.

The probabilities of the model were obtained from literature and are listed in Table I. The search was performed in February 2019 and was

limited to primary literature published in the English or Spanish language, human subjects, and children (birth to 5 years). The following engines were searched for the periods specified: MEDLINE from 1950 on, EMBASE from 1974 on, BIREME from 1980 on. To avoid missing any articles published we performed a search using Google search engine and we reviewed the first 100 results returned. Terms for these database searches included keywords closely matching the relevant medical field headings: *respiratory syncytial virus*, and *respiratory syncytial pneumovirus*. The authors (JAB, DG) reviewed all potentially relevant references independently and selected relevant publications. The study inclusion criteria were studies: (1) reporting the frequency or incidence of outcomes during the episode of community acquired, medically attended, severe RSV infection in children < 2 years for data analysis. (2) reporting data on laboratory confirmed diagnosis of RSV through enzyme-linked immunosorbent assay, polymerase chain reaction (PCR; Multiplex), immunofluorescence (IF), culture, direct fluorescent antibody test (DFA), or by relevant International Classification of diseases-9 (ICD-9) diagnosis codes. Population estimates of cases with RSV infection aged <2 years, was obtained from the National Institute of Health of Colombia (1).

Estimating resources and costs

To estimate resources and cost we conducted a prospective study in infants under two years of age admitted to the tertiary centers, in Rionegro due to an RSV infection (ICD-10 code: J21.0, according to the national clinical guideline of bronchiolitis¹⁷) from January 2015 to December 2016. Although the costs were derived from tertiary centers of Rionegro, all values as

Table I. Probabilities used in the model.

	Probability	CI 95%	Distribution
Hospitalization	0.014 ¹⁵	0.008-0.021	
Death	0.009 ¹⁵	0.003-0.014	Beta
Acute complications	0.144 ¹⁵	0.075-0.195	
Recurrent wheezing	0.281 ¹³	0.206-0.357	

detailed below were subjected to sensitivity analysis with a certain range and distribution in order to increase the external validity of our results.

Inclusion criteria were defined as children younger than two years of age admitted to the pediatric ward with a diagnosis of RSV confirmed using direct immunofluorescence (Light Diagnostics TM Respiratory Panel 1 DFA, Merck-Millipore Laboratory). Patients older than two years, without lower respiratory compromise, with positive bacterial cultures on admission, confirmed whooping cough, and those referred from another hospital center were excluded. After receiving informed consent from the parent or caregiver, the patient was interviewed and their electronic medical records were reviewed. We collected the following variables: age, sex, weight, height, signs, and symptoms at admission (e.g. fever, chest indrawing, chest auscultation abnormalities like rhonchi or crepitation), history of prematurity, bronchopulmonary dysplasia confirmed by a specialist physician on discharge from the neonatology unit, comorbidities (congenital heart disease, neurological disease), results of chest X-rays or other medical test, drugs and other treatments, and complications (pneumonia, atelectasis, sepsis). The clinical and sociodemographic characteristics of the patients from whom the cost information was extracted are presented in Table II.

The cost derivation follows a bottom-up approach based on the following formula: Number of "A" unit's x costs per unit "A" = Total cost of "A" units. Inpatient and outpatient costs, data of hospitalizations, and their costs were collected directly from medical invoices and health records. The direct costs considered in the analysis include: medical consultation at the emergency room, specialist referrals, chest physiotherapy, diagnosis support (laboratory, electrocardiogram, x-ray, etc.), medication (oxygen, nebulization, antibiotics, corticosteroids, bronchodilators, etc.) , medical devices, day-bed on the intensive care unit, and day-bed on the general medical ward. We used US dollars (Currency rate: US\$ 1.00 = COP\$

3,000) to express all costs in the study. For the evaluation of the indirect costs associated with the loss of productivity, the human capital method was used. In this, the cost-opportunity of the productivity loss at the workplace and the caregiver were assessed based on the minimum wage without including the transportation assistance for the year 2016 (U\$ 229.81 per month). Because all patients with RSV infection included were children, we assumed that at least one family member accompanied the patient permanently during hospitalization.

Table II. Sociodemographic and clinical characteristics of patients.

Variable. N (%)	N (%)
Age (months), median(ds)	5.66(0.38)
Male %(n)	113(58.55)
Premature birth	28(14.51)
Comorbidities (CHD, neurological)	11(5.71)
Atopy	21(10.88)
SpO2.median(ds)	88(0.93)
O2 support, n (%)	178(92.33)
Clinical & laboratory parameter	
Fever	53(27.46)
Chest indrawing	102(52.85)
Tachypnea	30(15.54)
Rhonchi	78(40.41)
Crepitation	36(18.65)
Leukocytosis (> 15.000/cm)	31(16.76)
Increased C-reactive protein (> 4 mg/lit)	59(44.81)
Chest X-ray	
normal	22(12.36)
peribronchial thickening	63(35.39)
hyperinflation	33(18.54)
atelectasis	5(2.81)
bilateral interstitial infiltrates	33(18.54)
alveolar infiltrates	22(12.36)
Length of hospital stay, median (range)	5.88(0.39)
Complications	
pneumonia	23(11.92)
Sepsis	9(4.66)
Atelectasis	5(2.59)
ICU	3(1.5)

CHD: congenital heart defect, ICU: intensive care unit

For the cost associated with transportation and food (does not include a stay), care was assumed to correspond to 50% of the day's cost for productivity loss at the workplace.

Data Analysis

Using the decision tree analysis, the cost of a patient with RSV infection was estimated. The validity of the estimates was evaluated, first by a tornado graph and the analysis of the permissible limit values to determine the variables with the greatest influence on the sensitivity analysis. In addition, a probabilistic sensitivity analysis was made using the Monte Carlo technique with a simulation of a hypothetical cohort of 10 000 patients in which each parameter varied randomly according to certain distributions (beta distribution in the case of probabilities, and gamma distribution in the case of costs) according to the recommendations of Briggs; to generate 95% confidence intervals (95% CI).¹⁸ The Tree age 3.5 statistical package was used in all analyses.

Results

Resource use and cost.

Overall, the diagnostic tests most frequently requested by the attending physicians were hemogram in 185 (95.85%) and chest radiography in 178 (92.22%) patients. The medications most often prescribed were nebulized or inhaled beta 2 agonists in 108 (55.96%), and nebulized hypertonic saline in 180 (93.26%) patients, see Table III. Overall, the major contributors to the hospitalization costs consisted of room costs (31.5%), drugs (21.8%) and indirect costs (14.9%). The medications with the highest average costs were nebulization with a hypertonic solution, systemic antibiotics, and parenteral fluids, see Table III. Diagnostic tests of both images and laboratory tests contributed to 9.32% of the costs per patient. Among these, chest radiography, blood cultures, C-reactive protein were the ones that most added to the costs per patient, see Table III.

Table III. Cost associated with RSV infection.

	Cost/patient/day	CI 95%	
Specialist referrals	10.457	10.117	10.798
Chest physiotherapy	5.049	4.805	5.293
Chest radiography	2.788	2.643	2.933
Others diagnostic imaging	0.005	0.000	0.022
Complete blood cell counts	1.190	1.134	1.247
RSV test	2.892	2.568	3.215
C-reactive protein and another test	3.988	3.914	4.063
Oxygen	1.463	1.382	1.544
Nebulization	20.558	19.665	21.451
Parenteral fluids	1.367	1.334	1.399
Systemic antibiotics	1.291	1.193	1.389
Systemic or inhaled corticosteroids	0.089	0.000	0.915
Bronchodilators	0.041	0.036	0.046
Medical devices	10.664	10.138	11.190
Hospital stay	23.925	22.745	25.106
The daily cost of the emergency ward	12.833	12.200	13.467
Indirect cost per day	17.236	16.386	18.087

Cost of an episode of RSV infection estimated by the model.

In the decision tree model, the mean cost per patient with RSV infection was US\$ 178.35 CI 95% (30.7-541.67 US\$). The final cost estimated by the model for each outcome can be seen in Table IV. In the probabilistic sensitivity analysis, the mean cost per patient with RSV infection was stable; being only sensitive to changes in the cost of recurrent wheezing, cost of outpatient visits and cost of hospitalizations, see Figure 2. In the other variables of costs and probabilities, there were no significant variations during this analysis.

Cost estimated by RSV infection in Colombia

Taking the total of national reports of RSV infection reported to the national surveillance system; and according to the prevalence of RSV infection found in local studies¹⁹; the total cost of RSV infection in children less than 2 years in Colombia were of US \$ 64 443 616 per year (CI 95% US\$11 092 902 – US\$195 722 867).

Discussion

The results of this study show the high economic impact of RSV-related bronchiolitis in a tropical country. The total cost of RSV infection in children less than two years in Colombia were of US \$ 64 443 616 per year; this is equivalent to more than 0.7% of the total health spending in Colombia for 2018.²⁰ Nevertheless, the proportion of cases of RSV infection in children under two years are less than 0.1% of the total of the event for any disease in Colombia.²¹ There is a clear imbalance between the number of patients treated and the cost that they generate, and the burden of expenses, perhaps mostly due to the use of medications or unjustified diagnostic tests.^{22,23}

The mean cost per patient with RSV infection were US\$ 178.35 CI 95% (30.7-541.67 US\$); this value being the most complete estimation of cost concerning this disease in any country in Latin America because we included indirect costs such as those associated with job loss

Table IV. Cost estimated by the model for each outcome.

	Cost/patient/day	SD	Distribution
Not hospitalized	171,73	228,92	
Hospitalized without long term complications	515,72	16,34	Gamma
Hospitalized with long term complications	840,52	189,79	

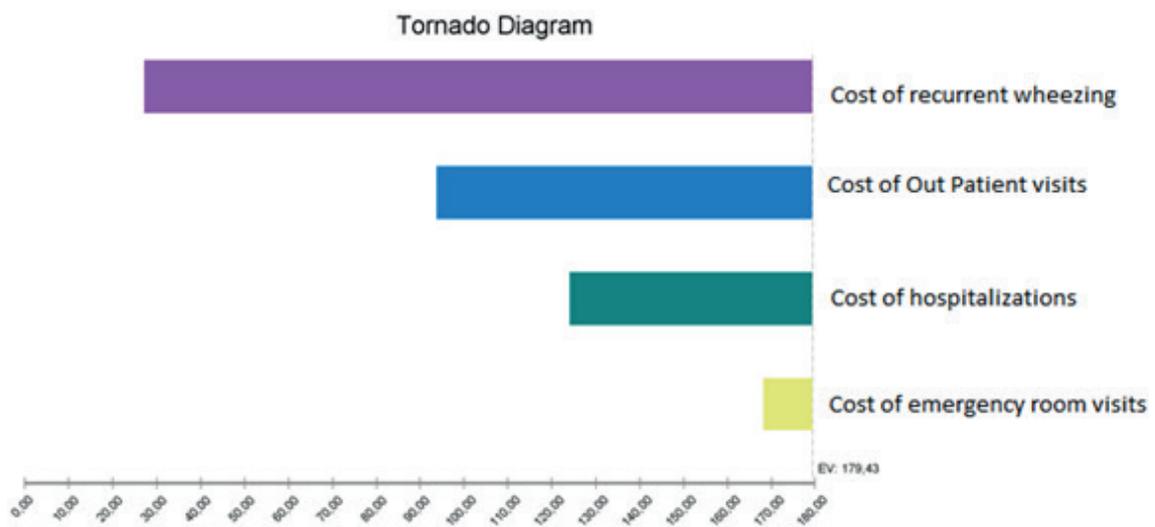


Fig. 2. Probabilistic sensitivity analysis.

and family expenses, and the cost of long term complications of RSV infection in the first two years. These values were similar to those reported from Bangladesh (US \$ 62)²⁴, China (US\$ 571)²⁵, and Chile (US \$ 632).⁴ The study from Bangladesh was made from a social perspective, and in Chile and China using a payer perspective. As is expected, due to the greater willingness to pay, our value per patient is lower than found in developed countries (For example: United States (US \$ 2664-3799)^{7,26}, United Kingdom (US \$ 3117)²⁷ and Finland (US \$ 955 1)²⁸). Not all previous studies were performed in the same population; most of them included the cost in children under five years and not only in the first two years. This may be difficult, in a practical sense, because the cases of RSV infection under two years are usually managed within clinical protocols of acute bronchiolitis in which the use of bronchodilators, corticosteroids, etc. are not recommended; while in older patients, especially if they have a history of wheezing episodes, are treated within asthma protocols which involve greater use of medications and diagnostic tests.^{29,30} In those studies that included only patients under one-year-old or preterm infants⁴; patients in which the initial treatment is usually more aggressive because of the risk of bacterial infection²⁹, their cost per patient also will be higher. For this reason, the values obtained in the different studies are not comparable, and it is not appropriate to infer differences in the resources used for health care in the diverse populations studied.

In respect to the impact of RSV infections concerning morbidity, RSV is frequently linked to hospital admissions, which results in a large burden to the health care system. For example, in 2015, around 45% of the hospitalizations and deaths occurred in RSV- in infants < 6 months.² Interventions to lower the prevalence and costs are deficient. No effective RSV-specific antivirals for active infection or preventive vaccines are available. RSV immune prophylaxis with targeted monoclonal antibodies (mAbs) is convenient for a limited population of high-

risk infants. The number of RSV products in development highlights the need for up-to-date information to estimate the impact of vaccines, antivirals, and mAb on disease burden, once approved.

In our study, the mean costs per patient with RSV infection were sensitive to changes in the cost of recurrent wheezing, cost of outpatient visits, and cost of hospitalizations. It is also widely documented in other populations studied, that variables such as the cost of long-term complications and wheezing are those that have the most impact on the total cost per patient.^{30,31} The cost of hospitalizations may be related to the increase of inappropriate use of antibiotics for RSV infections, which directly and indirectly increases the direct costs and days of hospital stay for patients.³² This highlights the need to mitigate, through early detection in patients at risk of developing wheezing to recurrence as a strategy to be evaluated for the cost containment in this population.

Indirect costs are the costs of those resources for which no payment is made, but for which there is an opportunity cost. Guidelines for economic evaluation studies in health care recommend the inclusion of indirect costs.³³ The addition of indirect costs usually had a substantial effect on the efficiency ratio, especially in pediatric diseases where hospitalization mobilizes the family, increasing the economic impact on society because of this disease. The non-inclusion of such costs otherwise leads to underestimating the real cost of the disease and the effect that preventive interventions may have to reduce the frequency and duration of hospitalizations. In our study, about 15% of the cost generated by the RSV infection is attributable to indirect costs. If we take into account that in Colombia there are about 361 332 annual cases of low acute respiratory infection due to RSV, according to the national epidemiological surveillance registries³⁴, and in our study the indirect costs are 17 dollars per day of hospitalization; this expense they represent more than 6 million dollars per day for our society. This fact highlights the impact that

preventive strategies may have on infections such as this one to reduce the opportunity cost and improve efficiency in the prioritization and allocation of health resources.

Our study has the following limitations: there may be differences in the costs used in this study when compared with the costs of other hospitals in Colombia. However, there is adequate adherence in our country to the use of health reference cost manuals, which means that there is low variability in the rates of each of the associated direct costs between each hospital.³⁵ All costs were subjected to probabilistic sensitivity analysis, and none of them showed a significant change in the result of the study. Likewise, the probabilities were not obtained directly from the Colombian population. However, they were extracted from the Latin American population, and were also evaluated in the probabilistic sensitivity analysis. Likewise, the time horizon of this study is 2 years, no temporary discount value was included in the costs due to the short follow-up time of the modeled cohort. Constant discount rates devalue the long-term health benefits of prevention strongly and are usually not recommended for modeling short duration acute events.

The RSV infection in Colombia generates a high economic burden on the health system. Generating comprehensive data on healthcare resource use and costs associated with RSV will help to provide valuable information for the development of cost-effectiveness models and help guide prevention strategies against RSV.

Acknowledgment

None to declare.

Ethical approval

The study protocol and their informed consent was reviewed and approved by the Institutional Review Board of Clinica Somer (No 281015) and the University of Antioquia (No 18/2015).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: JAB, DG, DS; data collection: JAB, DG, DS ; analysis and interpretation of results: JAB, DG, DS ; draft manuscript preparation: JAB, DG, Author. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

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