

# Disability-adjusted Life Years for respiratory syncytial virus in children under 2 years

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## Research article

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# Abstract

**BACKGROUND :** Respiratory syncytial virus infection is the leading cause of bronchiolitis in Colombia. There is growing evidence about the impact of Respiratory syncytial virus on society in terms of years of life lost due to this condition. The objective of the present study is to determine the Disability-Adjusted Life Years for respiratory syncytial virus in children under 2 years in Colombia **METHODS :** Data from the national epidemiological surveillance system were used to estimate DALYs, calculated from the sum of years of life lost and years lived with disability due to RSV infection in Colombia. A bootstrapped method with 10000 iterations was used to estimate each statistical parameter using the package DALY calculator in R. **RESULTS :** In 2019, 260 873 years of life (CI95% 208 180- 347 023) were lost due to RSV bronchiolitis in Colombian children under 2 years. The estimated rate was 20 DALYs / 1000 person-year (95% CI 16 – 27). **CONCLUSION :** This is the first report estimating the impact of RSV bronchiolitis morbidity and mortality in Colombia. The findings of the present study suggest that the actual burden and cost of bronchiolitis due to RSV is high. Prevention strategies, such as RSV vaccination, to reduce morbidity associated with RSV infection should be encouraged in our country.

## Background

Respiratory syncytial virus (RSV) is the most frequent cause of bronchiolitis worldwide. This virus causes 33.1 million episodes of RSV lower respiratory tract illness (LRTI), 3.2 million hospital admissions, and 59 600 in-hospital deaths in children younger than five years (1). Not all patients have the same risk of death. Certain high-risk groups, including premature infants, infants with bronchopulmonary dysplasia, hemodynamically significant congenital heart disease, immunocompromised conditions, or severe neuromuscular disease are prone to experience severe RSV with high morbidity and mortality rates (2, 3). The frequency or magnitude of association of these risk factors may change between different countries. The absence of seasonality, and the tropical climate, makes the behavior of RSV in Colombia differ from developed countries(4). In this sense, having complete epidemiological information in tropical countries is necessary to design of health policies.

Mortality does not give an entire representation of the burden of disease produced by individuals in different populations. The burden of disease is evaluated using the disability-adjusted life year (DALY), a time-based measure that link years of life lost due to premature mortality (YLLs) and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability (YLDs). One DALY means the loss of the equivalent of one year of full health(5). With this measure we can be estimated diseases that do not cause death but do cause disability. The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2015 estimated that lower respiratory tract infections caused 2.74 million deaths and 103.0 million disability-adjusted life-years (DALYs)(6). In this study DALYs, and deaths attributable to lower respiratory tract infections (LRTI). According to this study, in Colombia the DALYs attributable to lower respiratory tract infections in 2015 were 1.07 DALYs per 10000 in all ages. Despite, that previous studies had estimated the burden of disease of LRTI, in term of years of life lost by premature death or disability, theses report do not estimate it directly for RSV. A valid and consistent

description of the burden of disease is a great input to generate better health-policies and planning processes. Here, we estimated the disease burden of RSV infection in children less than 2 years in Colombia.

## Methods

### Design

Using the methods described by Murray and Lopez (5), we estimated the DALYs for RSV infection. DALYs were calculated for the most important health outcomes of this infection: RSV no complicated, RSV with or without acute mild or moderate complications (hypoxemia, atelectasis, pneumonia), RSV with severe acute complications (PICO admission, pneumothoraxes, pleural effusions, sepsis) and RSV infection with long term complications (recurrent wheezing). The study protocol was reviewed and approved by the Institutional Review Board of the University of Antioquia (No 18/2015).

### Model Parameters and Data Sources

To estimate the burden of disease we use incidences and mortality rates from comprehensive data reported by the national report of epidemiological surveillance system during 2017 (7). RSV is one of the notifiable diseases, it is mandatory for health providers, hospitals, and laboratories to report cases. The mortality data was validated with the data reported by the National Department of Statistics during the same time. Informed consent was not required because we used surveillance data without personal identifiers, **Table I**.

**Table 1.** Model inputs: morbidity probabilities used in base case and sensitivity analyses

| Model input   | Base case value | SA range for one-way sensitivity analyses | Source |
|---|-----------------|---|--------|
| <b>Probability</b>  |                 |   |        |
| Mortality by RSV in hospitalization                                   | 0,009           | 0,001-0,067                               | (7-12) |
| Mortality by RSV in pediatric intensive critical unit                 | 0,036           | 0,021-0,052                               |        |
| Incidence of acute complications in hospitalization                   | 0,131           | 0,101-0,202                               |        |
| Incidence of acute complications in pediatric intensive critical unit | 0,153           | 0,150-0,536                               |        |
| Probability of recurrent wheeze in RSV                                | 0,285           | 0,237-0,289                               |        |
| <b>Disability weight</b>  |                 |   |        |
| Mild or moderate lower respiratory infections                         | 0,051           | 0,032-0,074                               | (17)   |
| Severe lower respiratory infections                                   | 0,133           | 0,008-0,19                                |        |
| Recurrent wheeze  | 0,133           | 0,086-0,192                               |        |

SA : sensitivity analyses

To estimate the ranges of incidence and mortality rates, systematic review of studies previously published with Colombian patients was made. This search was performed in February 2019 and was

limited to published primary literature 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, we reviewed the first 100 results returned of this search. Terms for these database searches included keywords closely matching the relevant medical field headings: respiratory syncytial virus, and respiratory syncytial pneumovirus. The authors (JAB, JPS) reviewed all potentially relevant references independently and selected relevant publications. The inclusion criteria were observational studies, systematic reviews that reported the incidence or frequencies of clinical outcomes of a patient younger than 2 years with RSV infection, which included the Colombian or Latin American population. 27 studies were obtained of which 5 were included(8-12).

## Statistical analysis

The years of life lost by premature mortality were estimated, per outcome, by multiplying the number of deaths due to this outcome -in children with RSV under 2 years - by the number of years of expected remaining life at the age of death according to reference life tables recommended the manual of GBD studies(5). All estimates used the Colombian population in 2017 (13). The YLD per outcome was obtained by multiplying the number of cases –per outcome in children under 2 years with RSV infection - by both: the average duration of this outcome obtained from the literature (14), and respective disability weight derived from the 2015 GBD study, **table 1**. The internal consistency of each parameter was evaluated using the DISMOD II program (15) following the recommendations of manual for national studies of the WHO disease burden (5). To estimate the confidence interval around YLD, YLL, and DALYs, 10 000 iterations were made using a Monte Carlo simulation.. The DALYs was expressed both in absolute value and per 1000 person-years. Multi-way probabilistic sensitivity analysis was made using the standardized regression coefficient method (16). In this analysis was evaluated the percentage of change in the total estimate of DALYs, evaluating each of the variables within its range, (table 1) with a discount rate of 0 and 5%.

## Results

In 2019, we estimated that ~260 873 years of life (CI 95% 208 180- 347 023) were lost due to RSV infections in children under the age of 2 in Colombia. The estimated rate was 20 DALYs / 1 000 person-year (95% CI 16 – 27). 51-% (1 694 DALYs) were occurred in male children, and 63.19 % of DALYs affected children between 1 to 2 years of age (**Table 2**). 99% of DALYs represented years of life lost due to early death. Around 40% of DALYs (104632 DALYs) were generated by RSV with acute mild or moderate complications, followed by RSV with severe acute complications (31%), RSV infection with long term complications (16%) and uncomplicated RSV (12%), and this pattern was preserved in both age groups, **figure 1**.

**Table 2.** Distribution by sex and age of DALYs, YLL, YLD.

| Age        | DALYS |        | YLD |        | YLL   |        |
|------------|-------|--------|-----|--------|-------|--------|
|            | Men   | Female | Men | Female | Men   | Female |
| 0 - 1 year | 49037 | 46789  | 270 | 258    | 48766 | 46531  |
| 1- 2 year  | 84083 | 80386  | 579 | 553    | 83504 | 79833  |

Years of Adjusted Life by Disability (11), years of life lost due to premature death (1) and years of life lived with disability (YLD)

The results were robust in the sensitivity analysis. The percentage of change in the total estimate of DALYS did not exceed 25% with the variables analyzed; being the probability of death in children between 1-2 under the variable associated with the highest percentage of change in the DALYs (between 5-25%, of the final estimate). There were no significant variations in the discount rate, between 0 to 5% (Figure 2).

## Discussion

This is, to our knowledge, the first estimate of burden of RSV in children under age two years in Colombia. We found that only RSV infection in children less than 2 years generates very significant number of years of life lost, highlighting not only the importance of this etiological agent but also the usefulness of using DALYs to assess the true weight of a disease in society. RSV is not the only risk factor, there are environmental and individual variables that condition the development of the infection. Estimating the impact of potentially modifiable factors such as RSV, allows to guide prioritization processes in intervention efficiently

Respect to the difference to another burden of disease studies in our country, the global burden study estimated that LRTI accounts for around 14.1% of DALYs in children less than 4 years worldwide for example (17). In Colombia, this percentage was 6.35% (9.9 DALYs per 1000 in children less than 4 years and 3.98 DALYs per 1000 in children less than 2 years) (4). But our estimate is higher (was 20 DALYs / 1 000 person-year (95% CI 16 – 27), and only included RSV. The national burden of disease study used data from national health surveys. Our study examined the records of epidemiological surveillance. These records have a greater degree of completeness since they are mandatory in Colombia, and are completed by the physicians and this tendency of a discrepancy of results has been seen before with other estimation of DALYs (18, 19).

Otherwise, if RSV infection alone generates 20 DALYs for 1 000 children under 2 years of age, this disease would be only behind of low birth weight in the total estimation of DALYs in this age group. This finding is consistent with studies in the hospital setting where document the large amount of morbidity generated by RSV and acute bronchiolitis (1). Most of DALYs (63.19 %) were generated by children between 1-2 years, due to the greater amount of YLL lost, similar finding to other studies in Latin America (20). It's possible to explain this by a possible considerable delay in medical consultation of severe cases of RSV infection in older children , respect to younger children; due to attitude, more "relaxed" by parents with this patients . Further exist in older children a greater tendency to self-medication, aspects which affect the mortality rate (20).

When we compare our results with other estimations of DALYs of different diseases, RSV infection in children under age two years, generates more years of life lost than cervical cancer between 45-59 years (1.6 DALYs per 1 000 inhabitants), epilepsy between 30-44 years (1 DALYs per 1 000 inhabitants) and leukemia in children between 5-14 years (1 DALYs per 1 000 inhabitants)(4). This highlights the importance of generating specific burden of the disease studies by etiological agent, but also that it should encourage the development of vaccines, which according to our estimates would have a high population impact. Burden of disease studies should be a primary source for prioritization exercises in public health. Although in our continent even the use of health technology assessment and advanced statistical information is not the main input for decision-making, this type of estimations such as ours should encourage decision-makers to use evidence to make health decisions(21).

This study has limitations. First, we may have some degree of information bias and underestimation due to the use of data from the national surveillance and notification system (22). However, LRTI cases have florid symptomatology in this age group, often prompting medical attention. There are a global increasing in the reporting of cases to SIVIGILA has been noted (7), and in our sensitivity analysis , the final result of DALYs was not sensitive to the change in values of these probabilities, guaranteeing the robustness of the model. There are no specific "disability weights" for RSV infection. In this case, we used data reported for LRTI because in terms of mortality it does not differ from data presented by patients with other viruses in Colombia (14). In the sensitivity analysis, the percentage of change in the total estimate of DALYS did not exceed 25% within the variables analyzed.

## Conclusions

The burden of RSV bronchiolitis is a serious problem in Colombia, with a considerable social impact in terms of disability and mortality. Morbidity and mortality rates can be improved not only by effective prevention and promotion of public policies but also by improvements in the quality of health care services. Our results prompt evaluation of public health interventions and novel biological preventive strategies under evaluation to minimize the impact of this serious problem in Colombian children.

## Abbreviations

Years of life lived with disability (YLD)

National epidemiological surveillance system (SIVIGILA)

Global Burden of Disease study (GBD)

## Declarations

**Ethics approval and consent to participate:** This study was approved by the Institutional Review Board of University of Antioquia (2015-4690)

**Consent for publication:** Not Applicable

**Availability of Data and Materials** The raw data supporting our findings can be requested from CIEMTO : <http://ciemto.medicinaudea.co/contacto>

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**Authors' Contributions:** All the authors (JAB, JPSV, FPP) contributed in the same way from conception of the work to the publication of results. All Authors read and approved the manuscript

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# Figures

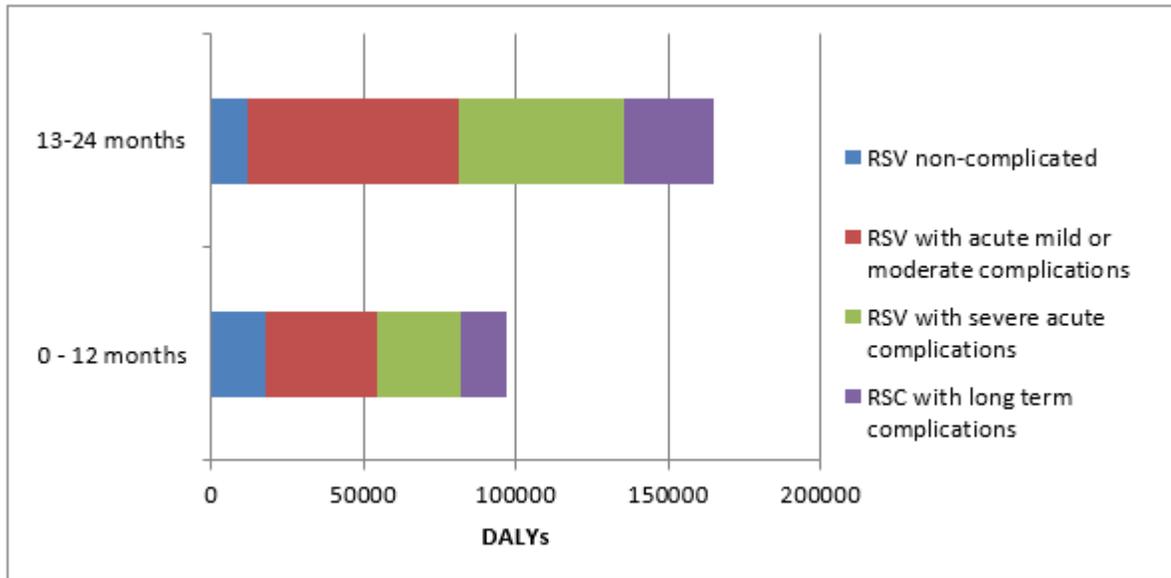


Figure 1

DALYs by outcome and age.

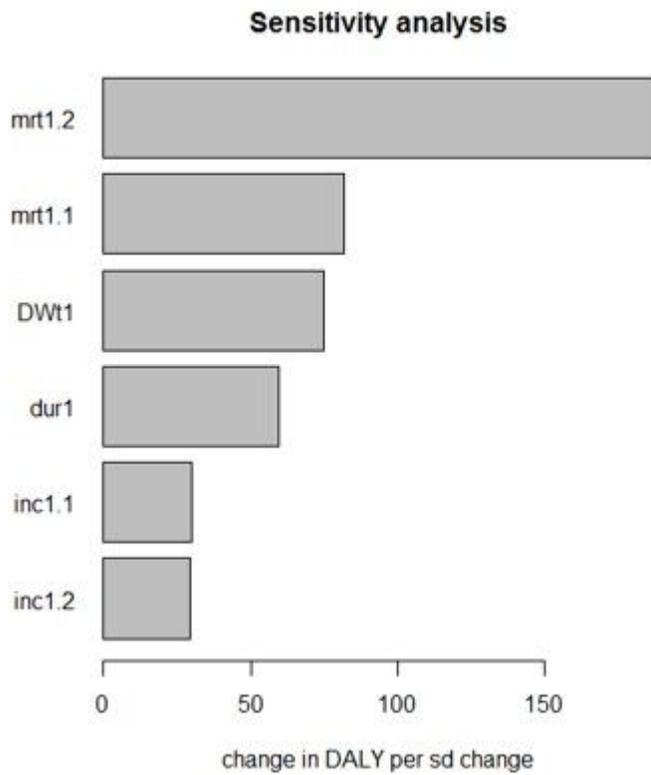


Figure 2

Results of sensitivity analysis: Mapped standardized regression coefficients