

Disability-adjusted Life Years for respiratory syncytial virus in Colombian children.

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Abstract

BACKGROUND Respiratory syncytial virus infection is the leading cause of bronchiolitis worldwide. However, little is known about the real impact of bronchiolitis 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 (1) 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 (IC 95% 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 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(2). 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 (3, 4). Approximately 96% of severe RSV cases occur in developing countries (5). Although the seasonality, risk factors, and clinical presentation of RSV in Colombia have been well characterized; and the burden of this disease in young children is unknown (1). 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 differentiate this burden by an etiological agent. 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

The burden of RSV bronchiolitis was estimated using records of LRTI and RSV infection in children younger than 2 years of age, reported to the national epidemiological surveillance system (SIVIGILA) during 2019. LRTI is one of the notifiable diseases and 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 period. Informed consent was not required because we used surveillance data without personal identifiers. The study was approved by the Institutional Review Board of the University of Antioquia (2015-4690).

This information was supplemented with review of clinical studies mainly in Colombian population to estimate the probabilities of the model, **Table I**. 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 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, JPS) reviewed all potentially relevant references independently and selected relevant publications. The study inclusion criteria were studies: reporting the frequency or incidence of outcomes during the episode of community acquired, medically attended, severe RSV in children < 2 years for data analysis. 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 or by relevant International Classification of diseases-9 (ICD-9) diagnosis codes. Exclusion criteria for the systematic review were studies: reporting data for children prophylaxes with palivizumab or other prevention strategies for RSV infection reporting data in special populations including children with cystic fibrosis or immunocompromised conditions; reporting data for nosocomial acquired RSV

Using the methods described by Murray and Lopez (8), 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, and pneumonia), RSV with severe acute complications (PICO admission, pneumothoraxes, pleural effusions, sepsis) and RSV infection with long term complications (recurrent wheezing).

The years of life lost by premature mortality (YLL) 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 of the global burden of disease study (9). All estimates used the Colombian population in 2017 (10). Next, 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 (11), 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 (12) following the recommendations of manual for national studies of the WHO disease burden (8). To estimate the uncertainty around YLD, YLD, and DALYs calculated before, we made 10 000 iterations in a Monte Carlo simulation, using a bootstrapped technique of DALY calculator package in R to obtain each confidence interval, with a discount rate of 3% and weighting by age. Multi-way probabilistic sensitivity analysis was made using the standardized regression coefficient method. (13).

Results

In 2019, we estimated that ~ 260 873 years of life (IC 95% 208180–347023) were lost due to RSV infections in children under the age of 2 in Colombia. The estimated rate was 20 DALYs / 1000 person-year (95% CI 16–27). 51 – 14% (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, Fig. 1.

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% (Fig. 2).

Discussion

This is, to our knowledge, the first estimate of the social burden of RSV in children under age two years in Colombia. We found that only RSV infection in children less than 2 years generates more DALYs than estimated previously for all LRTI in Colombia; differences at least from methodological view were due to differences in sources of information, but also show the real burden of disease of this infection in our society.

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 (1). 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) (14). But our estimate is higher (was 20 DALYs / 1000 person-year (95% CI 16–27), and only included RSV. The national burden of disease study used data from national health surveys while we examined the records of epidemiological surveillance. Our 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 (15, 16).

Otherwise, if RSV infection alone generates 20 DALYs for 1000 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 (5). Most of DALYs (63.19%) were generated by children between 1–2 years, due to the greater amount of YLL lost. Indeed, 99% of DALYs were caused by YLD which have more

weight in estimating the DALYs while YLL are not weighted by disability weights. Similarly, the mortality rates in Latin America by RSV, also were higher in children between 1–2 years (17). It's possible to explain this by a possible considerable delay in medical consultation of severe cases of RSV infection in this age group, respect to younger children; due to attitude, more "relaxed" by parents in this patients. Further a greater tendency to self-medication, aspects which affect the mortality rate (17).

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 1000 inhabitants), epilepsy between 30–44 years (1 DALYs per 1000 inhabitants) and leukemia in children between 5–14 years (1 DALYs per 1000 inhabitants)(14). 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(18).

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 (19). 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 (20), 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 (11). 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 cab 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.

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 your findings can be request to Instituto Nacional de Salud (<https://apps.ins.gov.co/pqr>)

Competing interests:

none to declare.

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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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none to declare.

Abbreviations:

Years of life lived with disability (YLD)

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Tables

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
Probability			
Mortality, given hospitalization	0,009	0,009-0,067	(21)
Mortality, given PICU admission	0,036	0,021-0,052	(22)
Acute complications , given hospitalization	0,131	0,101-0,202	(23)
Acute complications, given PICU admission	0,153	0,150-0,536	(24)
Probability of recurrent wheeze in RSV	0,285	0,237-0,286	(25)
Disability weight			
Moderate lower respiratory infections	0,051	0,032-0,074	
Severe lower respiratory infections	0,133	0,088-0,19	
Recurrent wheeze (Uncontrolled asthma)	0,133	0,086-0,192	(1, 26)

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)

Figures

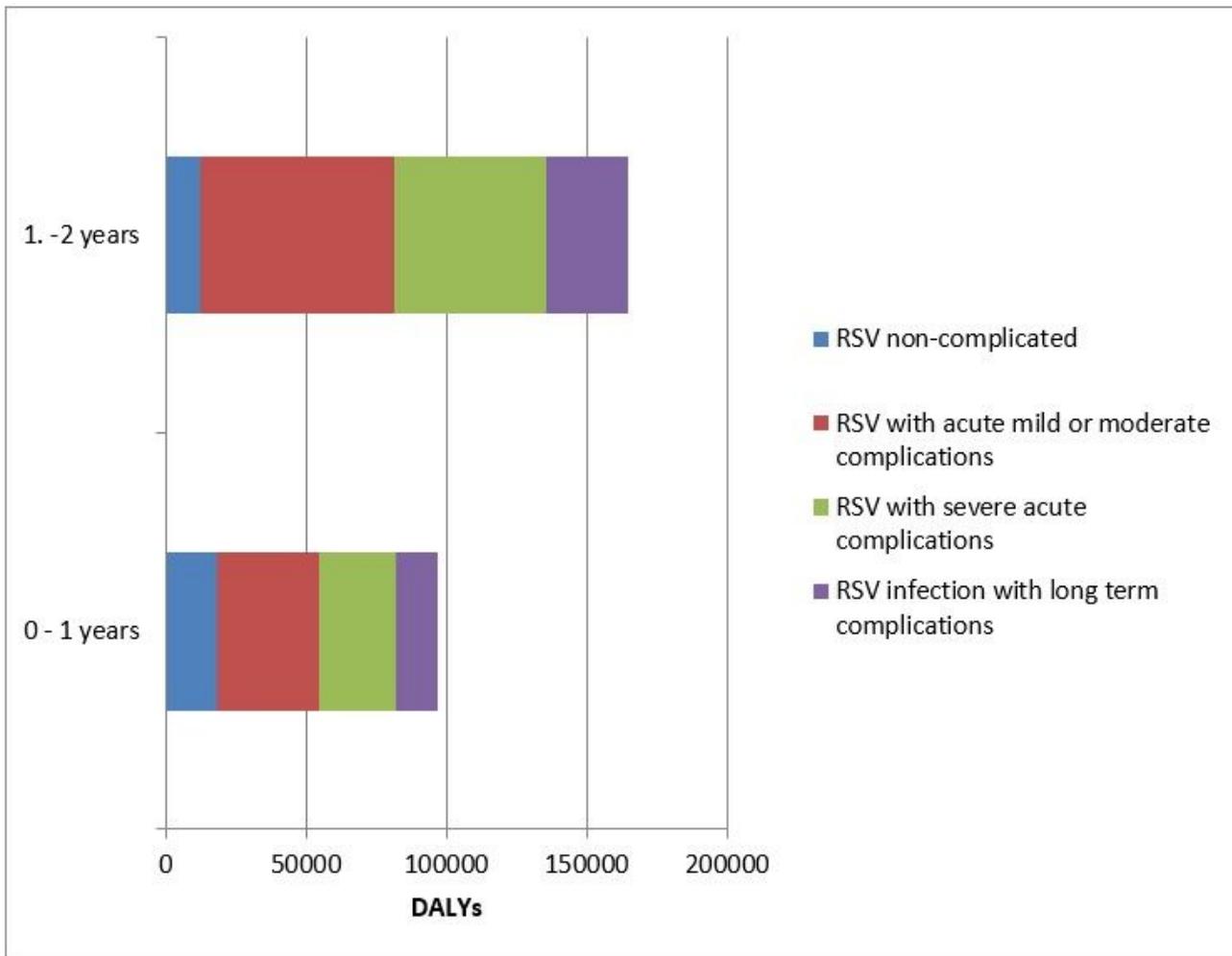


Figure 1

DALYs by outcome and age.

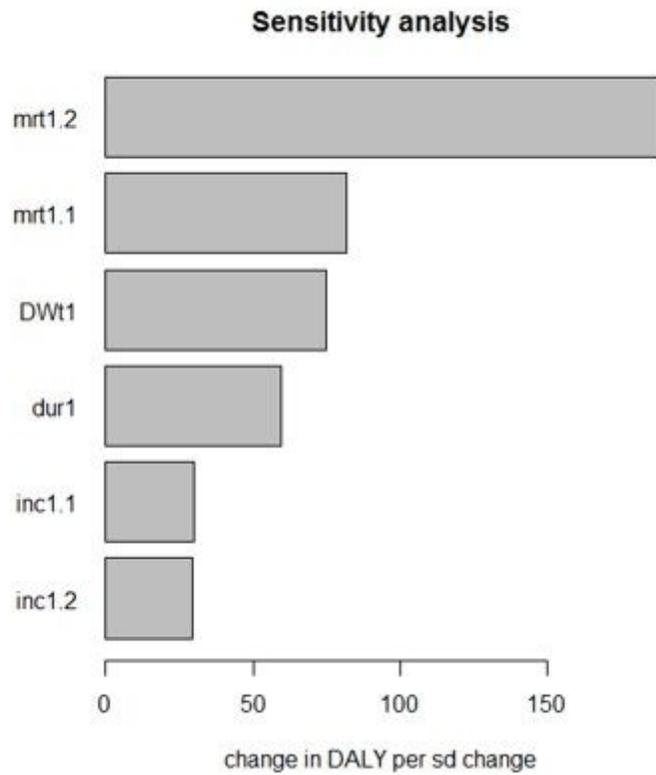


Figure 2

Results of sensitivity analysis: Mapped standardized regression coefficients mrt1.2 probability of death in children between 1-2 year mrt1.1 probability of death in children under 1 year