

The Burden of Respiratory Syncytial Virus Lower Respiratory Tract Disease in Infants in the United States: A Synthesis

Eric A. F. Simões¹

Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado, USA; and Department of Epidemiology, Colorado School of Public Health, Aurora, Colorado, USA

Keywords. costs; epidemiology; hospitalization; mortality.

Although pediatricians have long recognized that respiratory syncytial virus (RSV) is the single most important cause of lower respiratory tract infection (LRTI) in infants and young children, the most important cause of acute illness visits to their clinics, and the most important cause of hospitalizations during the respiratory season, we have been resigned for the last 4 decades to patiently waiting while other viral and bacterial diseases have been conquered by successful vaccines [1]. The seminal discovery of the stabilized prefusion form of the RSV F protein [2] occurring simultaneously with advances in immunology and structural biology have very quickly led to the development of long-acting monoclonal antibodies for infants [3–5] and vaccines for immunizing pregnant mothers [6, 7], both of which strategies target the prevention of RSV LRTI in infants. Palivizumab, a monoclonal antibody to be administered once a month [8, 9], although available since 1998, has only been used for prevention in select groups of high-risk infants and young children [10]. However, the vast majority of the burden of disease occurs in healthy full-term infants hitherto not eligible for this efficacious modality. Recent successful phase II and III studies of a long-acting monoclonal antibody (nirsevimab) [11–13] and phase II and III studies of maternal immunization [14, 15] provide imminent hope that we will at last be able to prevent severe disease caused by RSV in all infants. This paradigm shift necessitates a thorough review of the literature pertaining to the burden of disease, the cost to the

healthcare system and to families, and the morbidity and mortality caused by RSV in all infants, as presented in this supplement.

It has been estimated that globally in 2019 there were approximately 6.6 million episodes of RSV LRTI and 1.4 million RSV-associated acute lower respiratory infection hospitalizations in infants <6 months of age [16]. In the United States, a retrospective examination of the National Inpatient Sample (NIS) estimates that between October 2015 and December 2019, hospitalizations directly related to RSV accounted for 9.3% of all infant hospitalizations and were the most common cause of infant hospitalizations outside the birth hospitalization [17]. Given the low testing rate for RSV, the diagnosis of bronchiolitis could add another 3.7% of hospitalizations [17]. How does this translate to a burden of disease estimate in the United States?

The US Centers for Disease Control and Prevention, extrapolating data collected from 4 sentinel sites comprising the National Vaccine Surveillance Network (NVSN) and collecting data prospectively between 2000 and 2009, estimated that before the coronavirus disease (COVID) pandemic, there were over 33 000 hospitalizations and approximately 150 000 emergency room visits annually due to RSV [18]. A different modeling methodology utilizing retrospectively collected data from larger databases (NIS and the Nationwide Emergency Department Sample [NEDS]) as a numerator and the birth cohort data from the National Center for Health Statistics as the denominator arrives at a significantly higher probably more realistic, annual estimate of the burden—approximately 57 000 hospitalizations and 132 000 emergency room visits [19]. If one includes codes for bronchiolitis, the estimate for hospitalizations increases to almost 100 000 annually, whereas the burden in the emergency department (ED) increases to almost 300 000 a year, which is not surprising given the relative lack of testing for RSV in EDs [19]. The rate of hospitalization for Medicaid recipients is approximately 2 times higher than that for private payers, translating to 62% of RSV hospitalizations

Correspondence: Eric A. F. Simões, MBBS, DCH, MD, Department of Pediatrics, Children's Hospital Colorado, 13123 E. 16th Ave., Aurora, CO 80045, USA (eric.simoes@ucdenver.edu)

The Journal of Infectious Diseases® 2022;226(S2):S143–7

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<https://doi.org/10.1093/infdis/jiac211>

and 56% of ED visits occurring in infants insured with Medicaid, a major population utilizing health resources.

Although these studies give us a broad idea of the burden of RSV disease, how do these translate to actual rates of disease in the population? What is the burden in settings where we do not typically test for RSV, such as the ED or outpatient (OP) clinic? What proportion of hospitalized infants and children are admitted to the intensive care unit (ICU) for observation, and what proportion of those infants receive mechanical ventilation? Suh et al [20] conducted a systematic review of the literature to try and address these lacunae and provide us with rates. Surprisingly only 2 national studies had been conducted to estimate the rates of hospitalization, which varied between 22.0 and 25.2/1000 infants between 1997 and 1999 [21, 22]. A recent publication identified 25 studies estimating the rate of RSV-associated hospitalization [23]. In these studies, the annual rates varied between 8.4 and 40.8/1000 infants with a pooled rate of 19.4/1000. They found that passive, hospital-based surveillance studies underestimate those obtained from administrative claims data by almost half (11.0 vs 21.4/1000 infants). It was estimated that in the 2020 birth cohort, there were approximately 80 000 RSV hospitalizations in the first 6 months of life [23], a rate closer to the estimates of 100 000 RSV hospitalizations in the first year of life using the NIS data [19]. Studies show that between 15% and 20% of infants hospitalized with RSV spend a portion of their stay in the ICU, a little over half of whom receive mechanical ventilation. This rate drops somewhat in the second half of the first year of life. There is a lot of heterogeneity in the data based on the populations studied, but the exact proportions still have enough uncertainty that one cannot make an estimate per thousand population with any degree of accuracy [19, 24].

Not surprisingly, there were no nationally available data on ED usage or OP burden of RSV disease [19], probably due to the low rates of testing in these locations [25]. Gantenberg et al [26] used 3 separate claims databases (Marketscan Commercial, Marketscan Medicaid, and Optum Clinformatics) to include a birth cohort of almost 2 million infants born between April 2016 and February 2020 to try and address this lacuna. Their estimates used specific (RSV) and more sensitive (bronchiolitis) codes to estimate the burden of medically attended LRTI in the OP, ED, and inpatient settings. They estimate the overall medically attended LRTI burden of disease varied between 48.9 and 73.2/1000 infants during the first RSV season using the specific definition, and that increased 3-fold to 124.0–183.3/1000 infants using the more sensitive definition. Of these visits, 80% occurred in full-term babies [26]. These latter numbers reflect what most pediatricians see in practice, because approximately 1 of 5 to 1 of 4 (20%–25%) of their practices' babies born around the RSV season come in for a diagnosis of bronchiolitis, and most of them are full-term babies.

At the heart of this uncertainty lies the variability in testing for RSV and the coding for laboratory-confirmed RSV bronchiolitis. Undoubtedly, it is the dictum “testing makes no difference to the management of the patient” that drives this variability. The systematic literature review of RSV laboratory testing practices thus reflects the vast variability in testing [25]. As would be expected, testing occurs more frequently in the inpatient setting than in the ED or OP settings. There were only 2 Kaiser Permanente studies that compared testing across all management settings. They found that 83%–85% of inpatients with bronchiolitis were tested compared with 29% of ED patients and 25% of OP patients [27, 28]. The NVSN sites tested between 7% and 24% of inpatient samples depending on the age (2009), which increased to 19%–60% in the 2015–2016 timeframe [18], the lowest values being in the oldest children. Most other sites tested between 30% and 70% of admitted subjects. In contrast, except for outliers, in EDs approximately 27%–32% and in OPs approximately 15%–20% of infants' samples with LRTI were tested in reported studies [25]. In most private and public practices around the country, pediatricians and family practitioners rarely have access to nucleic acid tests in their offices, and for most pediatricians, the compensation offered for rapid testing—if it is offered at all—does not appear to economically justify its use. During the RSV season, most clinical bronchiolitis in doctors' offices is ascribed to RSV without testing, which it probably is. Before the COVID pandemic, nucleic acid tests for RSV that were quickly becoming the gold standard were expensive, explaining the relative paucity of data for this very common disease in the OP and ED settings [29]. With the first wave of the pandemic in 2020, it became clear that testing for respiratory viruses was important in the OP setting. Quickly testing for severe acute respiratory syndrome coronavirus 2, influenza, and RSV became available in various combinations, and such testing is increasingly being used to detect these pathogens, even in the OP setting, in children with upper respiratory tract signs. This availability is likely to influence future estimates of disease burden.

No accounting of the burden of RSV disease is complete without an examination of its impact on the caregiver and the family taking care of the infant and on the direct and indirect costs to society. In this supplement, Glaser et al [30] assess the evidence on the impact of RSV on the quality of life of children under 5 years of age. They found 7 studies, only 2 of which were focused on preterm babies [31, 32] and could be used to calculate the net quality-adjusted life years per nonfatal episode of RSV in the first 60 days of life. These were estimated to be 0.0169 for the child, 0.0031 for the caregiver, 0.0200 for the child and caregiver dyad, and 0.0067 for the family, all directly attributable to RSV. There were no studies in full-term infants.

A review of 17 recent studies (after 2014) on the economic costs of the burden of RSV revealed a mean cost of RSV

hospitalization of approximately \$12 000, resulting in an estimated annual aggregate cost of \$472 million, with full-term babies accounting for 70% of these costs [33]. When broken down by payer, the overall mean cost to commercial payers was \$15 289 compared with \$10 394 for Medicaid, although by sheer volume Medicaid financed 61% of the aggregate cost. The average cost of RSV hospitalizations per birth was calculated to be \$124 per birth/year. There were only 4 studies reporting RSV-associated costs in ambulatory settings. The mean cost for an ED or urgent care visit was \$501, and the mean OP-associated cost was \$73/visit. It is clear that the major cost burden is based on hospitalization.

A separate analysis using a static decision-analytic model that arrived at a considerably higher economic cost of RSV \$1.2 billion showed that RSV hospitalization—despite contributing only 9% of the annual 529 915 healthcare case burden of RSV LRTI—resulted in 92% of the costs (27% hospitalization, 44% ICU admission, and 21% mechanical ventilation). In contrast, primary care and ED visits, although contributing to 91% of the healthcare burden, only accounted for 8% of the costs [34]. Because infant Medicaid recipients shoulder a major burden of RSV disease [19] and the associated costs [33], it is imperative that effective prevention measures also be offered to these infants [35].

Although globally RSV is the most important cause of mortality from LRTI in the pneumococcal vaccine era that is often underrecognized, most of these deaths occur in developing countries [16]. Although the case-fatality ratios from RSV vary between 0.5% and 7% in developing countries [16], these ratios vary from 0.04% to 0.90% in the United States based on large-scale or nationwide data [36]. A systematic review of studies reporting estimates of RSV mortality estimated that RSV deaths occurred at a rate of 8.4/million live births and bronchiolitis deaths varied between 20 and 94/million live births [36]. These estimates come from data extrapolated from a single nationwide study examining RSV deaths between 2004 and 2007 [37]. Reichert et al [38] included more recent nationwide data (1999–2018) that used the National Vital Statistics System to link birth and death certificates, estimating 561 RSV deaths and 1603 bronchiolitis deaths. This translates to approximately 7 and 20 per million live births, respectively. Strikingly, 54% of these deaths were in full-term babies and 21%–54% occurred outside the inpatient setting [38] or at home [39, 40]. A disproportionate percentage of these occurred in infants on Medicaid (62%) and in Black (26%) and Hispanic/Latino infants (22%) [38]. Using death certificate data from the same time period, Hansen et al [40] estimate that there are 96 RSV-related infant deaths in the United States annually.

In summary, we have learned from this series of articles that the burden of RSV hospitalization in US children is significant, causing between 9% and 12% of all nonbirth hospitalizations and resulting in between 80, 000 and 100, 000 hospitalizations

annually and almost 3 times that number of visits to the ED. Medicaid-insured infants have approximately 2 times the rate of hospitalization of those with private payers, accounting for 62% of RSV hospitalizations and 56% of ED visits. Of all children hospitalized, between 15% and 20% go to the ICU and approximately half of these receive mechanical ventilation, but there is enough heterogeneity in the data that these are only estimates. Given the uncertainty around RSV testing in the OP and ED situations and adjusting for the sensitivity, it has been estimated that the overall burden of medically attended RSV LRTI in infants varies between 50 and 180/1000, 80% of which occurs in full-term infants. The average cost of an RSV hospitalization is approximately \$12 000, and even though Medicaid pays approximately 2 of 3 of what private payers pay to hospitals and healthcare systems, because of the high rate of hospitalization, Medicaid covers approximately 61% of the aggregate \$472 million average cost of hospitalizations. Unfortunately infants on Medicaid account for a disproportionate portion (62%) of the RSV deaths as well.

Respiratory syncytial virus prevention is very close to becoming a reality for every child. Given the significant inequity that the less socioeconomically advantaged among us suffer, it is essential to ensure that they benefit from these preventive strategies.

Notes

Financial support. We received minor copyediting support from Sanofi.

Supplement sponsorship. This article appears as part of the supplement “Respiratory Syncytial Virus Disease Among US Infants,” sponsored by Sanofi and AstraZeneca.

Potential conflicts of interest. E. A. F. S. reports the following: grants and consulting fees to the institution from Merck & Co. and Pfizer Inc; grants to the institution from Astra Zeneca Inc., Roche Pharmaceuticals, and Johnson and Johnson; consulting fees to the institution from Sanofi, Cidara Therapeutics, Adiago Therapeutics Inc, and Nuance Pharmaceuticals; manuscript writing support from Sanofi and Astra Zeneca Inc.; support for attending a meeting at Astra Zeneca Inc. and participation on a Data and Safety Monitoring Board from Abbvie Inc., GlaxoSmithKline plc, and the Bill & Melinda Gates Foundation, all outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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