Impact of Respiratory Syncytial Virus on Child, Caregiver, and Family Quality of Life in the United States: Systematic Literature Review and Analysis

Elizabeth L. Glaser,1,6 Dhvani Hariharan,1,6 Diana M. Bowser,1,6 Raissa M. Gervasio,1,6 Katharine R. Rowlands,1,6 Lauren Buckley,1 Christopher B. Nelson,2,6,8 and Donald S. Shepard3,6

1The Heller School for Social Policy and Management, Brandeis University, Waltham, Massachusetts, USA; and 2Sanofi, Swiftwater, Pennsylvania, USA

Background. Respiratory syncytial virus (RSV), a leading cause of lower respiratory tract infection in US children, reduces quality of life (QOL) of children, their caregivers, and families.

Methods. We conducted a systematic literature review in PubMed, EconLit, and other databases in the United States of articles published since 2000, derived utility lost per RSV episode from cohort studies, and performed a systematic analysis.

Results. From 2262 unique citations, 35 received full-text review and 7 met the inclusion criteria (2 cohort studies, 4 modeling studies, and 1 synthesis). Pooled data from the 2 cohort studies (both containing only hospitalized premature infants) gave quality-adjusted life-year (QALY) losses per episode of 0.0173 at day 38. From the cohort study that also assessed caregivers’ QOL, we calculated net QALYs lost directly attributable to RSV per nonfatal episode from onset to 60 days after onset for the child, caregiver, child-and-caregiver dyad of 0.0169 (167% over prematurity alone), 0.0031, and 0.0200, respectively.

Conclusion. Published data on QOL of children in the United States with RSV are scarce and consider only premature hospitalized infants, whereas most RSV episodes occur in children who were born at term and were otherwise healthy. QOL studies are needed beyond hospitalized premature infants.

Keywords. caregiver; infant; premature; quality-adjusted life-year (QALYs); quality of life; respiratory syncytial virus (RSV); systematic review; United States; utility.

Respiratory syncytial virus (RSV) is a leading cause of respiratory infection in childhood, and a major cause of hospitalization, especially those aged ≤6 months [1], with most children in the United States infected with RSV by age 3 years [2]. In a healthy child, RSV infection typically manifests as a runny nose, fever, cough, and wheezing, which resolve without long-term sequelae [3]. However, in 1%–2% of children, the infection will progress to an acute lower respiratory tract infection (LRTI), such as bronchiolitis or pneumonia, requiring hospitalization [4, 5] and possible long-term consequences [6, 7].

The quality of life (QOL) of young children with RSV can be adversely affected by discomfort, cough, or difficulty feeding [8]. In hospitalized children there would be short-term consequences to emotional and physical well-being in the acute period, with a subset experiencing long-term changes in QOL due to asthma [9]. Parents and caregivers may also experience emotional distress, loss of sleep, and decreased ability to attend to work or meet the needs of other family members [10].

Although existing statistics report rates of hospitalizations and medical services for RSV, there are few indicators of the impact of RSV on child and caregiver QOL via patient-reported outcome measures (PROM) or health utilities as there are few validated PROM instruments for young children [11–14].

The US literature on QOL in RSV-affected infants contains 2 observational cohort studies, 4 simulation models, and 1 synthesis. The simulations assess the efficacy of monoclonal antibody treatments for reducing the risk of severe RSV infection featuring utilities derived from other diseases or age groups rather than incorporating QOL estimates from children with RSV. With the exception of the synthesis, the studies examine the impact of RSV among a small group: those children at high risk for the disease [15, 16]. A systematic review on the QOL of children with RSV can provide high-quality evidence to inform future research, prevention and treatment, and economic analyses. Here, we summarize and assess the evidence of the consequences of RSV infection on QOL in children <60 months of age in the United States.
METHODS

Overview
We conducted a systematic literature review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17, 18]. The protocol was submitted to the Prospective Register of Systematic Reviews prior to the review (PROSPERO ID: CRD42020168469) and was posted online on 28 April 2020 [19]. The review was split into 2 substudies (ie, costs and QOL). This review focuses on QOL.

Information Sources, Search Strategy, and Selection Criteria
We identified all published data in English from 1 January 2000 through 2 August 2021, from 11 sources (Supplementary Materials 1). Any economic study of acute RSV, assessment of QOL, use of QOL instruments (eg, EuroQol, PedsQL), and measurement of quality-adjusted life-years (QALYs), and data from clinical trials, observational studies, population studies, claims analyses, or case series in children <60 months old in the United States and modelling studies were included (Supplementary Materials 2).

Study Selection, Data Extraction, and Quality Assessment
Two reviewers (E. L. G. and D. H.) independently conducted the screening and data extraction. Any conflicts were resolved through discussion with a senior investigator (D. S. S.). The data on QOL before and after episode onset, utilities or QOL, and QOL instruments were extracted. From economic evaluation studies, the data on perspective, time horizon, discounting, treatment, tools, or measures utilized, valuation of preference-based outcomes, and funding source were extracted. The quality of included studies was assessed using an adapted version of a quality assessment tool devised by Gheorghe et al [20] as outlined in the Supplementary Materials 3. Our adapted tool was used to conduct a critical appraisal of the eligible QOL evaluations. In doing so, our work modified the published study protocol, which proposed the Joanna Briggs Institute Critical Appraisal Checklist for Economic Evaluations for risk of bias assessment, as that Checklist proved not to be well suited for the studies of QOL and health utilities.

Data Synthesis
Given the small number and heterogeneity of the included studies, the planned meta-analysis including studies that used health utilities or QOL scores could not be conducted. Instead, using the 2 prospective observational cohort studies (Leidy et al [21], which had a control group, and Pokrzywinski et al [22]), we conducted systematic analyses to derive utility lost from RSV for premature children and their caregivers. The data collection timelines of the 2 studies are explained in the Supplementary Materials 3.

In the study of premature infants with RSV and controls [21], we converted the global rating of health scale (range, 0–100) to a scale ranging from 0 to 1 for rating utilities. To calculate QALYs, we multiplied the average health utilities in each group by a 60-day duration as a portion of a year (365.25 days) and found the difference between the estimated QALYs in symptomatic RSV-infected and -uninfected groups for the children, caregivers, and their families. We noted that the modeling paper by Weiner et al [23] used an approach roughly similar to ours. However, Weiner et al did not provide the details of their methods and apparently did not include the fact that the control group [21] began with a QOL of less than 1.00.

We pooled and smoothed the data from 2 RSV cohort studies [21, 22] and computed cumulative QALY losses from the date of admission through each available date of follow-up. Our base case analysis focused on 30 days from hospital discharge as a period that both empirical studies included and best reflected the acute portion of the illness. Additional cumulative analyses considered only the inpatient period and the maximum follow-up available. For the 2 cohorts of premature infants [21, 22] and the control group in 1 [21], we performed linear interpolation between the assessments to generate estimates for each day of the observation period. Supplementary Materials 3 detail the methods of pooling, data smoothing, and sensitivity analyses.

RESULTS

Literature Search Results
A total of 3353 studies were identified through database searches and, after removal of duplicates, 2262 were considered for screening. We excluded 2227 records, assessing 35 full-text articles for eligibility. Of these, 6 articles met our criteria. One additional study was identified separately. Together, 7 studies were included in our final review [21–27] from the reference search of studies screened and met our inclusion criteria (Figure 1 and Table 1).

Study Characteristics
Of the 7 studies, 6 [21, 22, 24–27] focused on RSV risk in premature infants or infants with congenital conditions, whereas 1 was a systematic analysis of children <5 years of age with LRTI. Two of the 7 studies [21, 22] used preference elicitation scales and provided QOL estimates. Four of the 7 studies were cost-utility analyses modeling QALYs to estimate the incremental cost-effectiveness ratio of prophylaxis with a monoclonal antibody or a hypothetical vaccine compared to no prophylaxis [23, 24, 26, 27]. The final included study, a synthesis, focused on population estimates of disability adjusted life years (DALYs) lost to LRTI [25]. As RSV is one of the principal causes of LRTI, the synthesis offers useful insights on RSV. As DALYs are a complement to QALYs, DALYs equal QALYs lost. These 7 studies were published from 2004 through 2019 (median of 2012).
Assessment of Quality of Included Studies

Using the adapted quality assessment tool, the selected studies were assessed for their source or form of QOL elicitation, relevance of the age of the population assessed, and the relevance of the location of the study. Table 2 lists the studies and their rating. Of the 7 studies, 5 were in the medium-to-high categories across all 3 parameters [21–23, 26, 27]. Specifically, 2 were highly rated across all 3 parameters because they focused on RSV events in US infants ≤30 months of age and estimated the influence on the QOL of children using a numerical rating scale elicited from caregiver proxies and also elicited caregiver-specific QOL directly. Although all included studies explicitly stated that the focus population was in the US, 4 citations [24, 25, 27, 28] were downgraded in rating because their model utilities were derived from respondents in countries outside the US, and their utilities were based on LRTI overall, not RSV specifically.

Direct Elicitation Studies

Two studies obtained utilities empirically via parent proxies to assess the consequences of RSV on hospitalized infants and young children with a history of prematurity (weeks’ gestational age [wGA] 29–35). In Leidy et al’s study [21], the RSV-hospitalized group of 46 children had a mean chronological age of 10.2 (SD 9.3) months and a hospital length of stay of 5.8 (SD 8.0) days, while the 212 enrollees in Pokrzywinski et al’s study [22] were slightly younger in age (3 [SD 3] months). The latter cohort had a longer hospital length of stay (8 [SD 9] days), with 51% admitted to intensive care, of whom 21% required mechanical ventilation. Leidy et al [21] included a comparator group with age and geographically matched uninfected controls.

The primary outcomes of both studies included RSV severity and caregiver’s rating of infant health and functional status, caregiver health, stress, and anxiety, and family functioning. The caregivers were questioned during the period of acute illness and after hospitalization. The age-matched controls were questioned during a baseline period and 60 days later. Relevant to measurement of QOL, both studies used a global rating of health numerical rating scale (range, 0–100, where 0 = the worst health imaginable and 100 = the best health imaginable) to rate current health. The parents were also asked to rate the child’s health before onset of RSV.

In Leidy et al’s study [21], the mean global rating of health in the RSV infected groups was 77.0, which was significantly below the score of 92.5 in the control group during the baseline period (P < .05). After 60 days, these scores changed to 87.0 and 95.0 in the RSV and control groups, respectively, indicating

Figure 1. PRISMA flowchart. Abbreviations: CDSR, Cochrane Database of Systematic Reviews; DARE, Database of Abstracts of Reviews of Effects; HTA, Technology Assessment Database; NHS EED, National Health Service Economic Evaluation Database; PEDE, Pediatric Economic Database Evaluation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ProQuest D&T, ProQuest Dissertations and Theses Global.
| Author, Year | Country | Study Type | Study Cohort | Comparator | Cohort Characteristics | Perspective | Time Horizon | Discounting |
|-------------|---------|------------|--------------|------------|------------------------|-------------|--------------|-------------|
| Leidy, 2005[21] | United States | Case-control study | Hospitalized infants with RSV | Infants without RSV hospitalization | RSV group: RSV-hospitalized infants and children ≤30 mo of age with a history of prematurity (≤35 wGA), admitted with a laboratory-confirmed diagnosis of RSV-related acute LRTI; control group: age-matched infants in the same location (5 US hospitals) with no RSV hospitalization | NA | Assessment timing: data for the RSV group were gathered within 48 h after admission to the hospital at days 4, 14, 21, and 60 after hospital discharge. Data for the control group were gathered at a control baseline time and at 60 d thereafter | NA |
| Pokrzywinski, 2019[22] | United States | Survey-based prospective cohort study | Hospitalized infants with RSV | None | Preterm infants 29–35 wGA and aged <12 mo hospitalized for laboratory-confirmed RSV disease who did not receive RSV immunoprophylaxis | NA | 30 d after discharge | NA |
| GBD Collaborators, 2017[25] | Global, with country-specific results | Systematic analysis of LRTI based on real-world data and posterior estimates | Children <5 y and children all ages with LRTI (HiB, pneumococcal pneumonia, influenza, RSV)/ | None | LRTI cases stratified by country, sex, age, and year | NA | Cross-sectional data for 2015 | NA |
| Yount, 2004[27] | United States | Economic evaluation and modeling study | Prophylaxis with palivizumab | No palivizumab | Hypothetical cohort of 10 000 infants with CHD | Societal perspective | Lifetime | Cost and QALYs discounted at 3% |
| Elhassan, 2006[24] | United States | Economic evaluation and modeling study | Prophylaxis with palivizumab | No palivizumab | Hypothetical cohort of premature infants born at 26–32 wGA without CLD, discharged from the neonatal intensive care unit at 36 wGA | Societal perspective | Analyses without asthma: 1 y time horizon from birth; analyses with asthma: 8 y in the base-case analysis, and varied up to 10 y in sensitivity analyses | Cost and QALYs discounted at 3% |
| Weiner, 2012[23] | United States | Economic evaluation and modeling study | Prophylaxis with palivizumab | No palivizumab | Hypothetical cohort of premature infants born at 26–32 wGA without CLD, discharged from the neonatal intensive care unit at 36 wGA | Societal perspective | Lifetime | Cost and QALYs discounted at 3% |
| Régnier, 2013[26] | United States | Economic evaluation and modeling study | Infants hypothetically vaccinated for RSV | Infants not vaccinated for RSV | A hypothetical cohort of newborn infants | Societal perspective | 5 y–lifetime* | Cost and QALYs discounted at 3% |

Abbreviations: AAP, American Academy of Pediatrics; CA, chronological age; CHD, congenital heart disease; CLD, chronic lung disease; HiB, Haemophilus influenzae type b; LRTI, lower respiratory tract infection; NA, not applicable; QALY, quality-adjusted life-year; RSV, respiratory syncytial virus; wGA, weeks’ gestational age.

*5 years after birth for health care utilization, 10 years for the impact on asthma, and lifetime for loss of productivity due to premature death.
The base case utility losses for hospitalization and evaluated the immediate impact of RSV during and after hospitalization. The base case utility losses for hospitalization and for a 60-day postrecovery period were 0.3972 and 0.0911, respectively (Table 3). The change in QALYs ranged from 0.014 to 0.0539, based on extent of prematurity, chronological age at time of RSV, and risk factors.

Régnier [26] used a hypothetical cohort of infants to assess the cost utility of a theoretical vaccination versus prophylaxis with palivizumab in high-risk children aged <5 years. The study included RSV-related hospitalizations and emergency department, outpatient, and primary care provider visits, along with mortality and long-term sequelae. The study obtained health utilities and QALY losses from Lee et al [32], who reported utilities of 0.78 for mild cough, 0.67 for severe cough, and 0.58 for respiratory complications using short-term time trade-off assessment of pertussis in adolescents and adults. Severe cough and complications were categorized as emergency department or inpatient events, and therefore the authors in this study assumed 0.78 to be the utility for an outpatient RSV event (Table 3). The study reported that 77% of hospitalizations occurred in children aged <12 months, with 57% in children aged <6 months.

Data Synthesis
Using data derived from Leidy et al [21], the QALY losses directly attributable to RSV for the infant, caregiver, and family were 0.0169, 0.0031, and 0.0067, respectively (Table 4). We also calculated a combined metric for child and caregiver, and the estimated QALY loss due to RSV for this dyad was

Table 2. Quality Assessment of Included Studiesa

| Author, Year [ref] | Source/Form of Elicitation | Relevance of Population | Summary Score |
|---------------------|---------------------------|-------------------------|---------------|
| Leidy, 2005 [21]    | High                      | Age Location            | High          |
| Pokrzywinski, 2019  | High                      | Age Location            | High          |
| GBD Collaborators, 2017 [25] | Medium             | Age Location            | High/medium   |
| Yount, 2004 [27]    | Medium                    | Location                | High/medium   |
| Elhassan, 2006 [24] | Medium                    | Location                | High/medium   |
| Weiner, 2012 [23]   | Medium                    | Location                | High/medium   |
| Régnier, 2013 [26]  | Medium                    | Location                | High/medium   |

*aAssessment tool was adapted from Gheorghe et al [20].

bThe studies by GBD Collaborators [25], Yount [27], and Elhassan [24] were given a lower rating for location because their utility values were derived from studies based globally or in Canada, not the United States. All other included studies explicitly stated that the focus population was in the United States.

improved health in the RSV group but lower scores compared with those of age-matched controls. Of note, the average score in the control group was 95.0, about 5% below the score for perfect health (100) (Table 3). In Pokrzywinski et al’s study [22], at hospital discharge the mean infant health score was 64.3 (SD 26.9)—lower than those of the RSV-infected infants in Leidy et al’s study (Table 3).

Global Systematic Analysis Study
GBD Collaborators estimated LRTI-associated mortality and morbidity for 4 etiologies, including RSV, across 195 countries by age using the Global Burden of Disease (GBD) 2015 study [25]. This study estimated 47 000 disability-adjusted lifeyears lost due to LRTI in the United States in children aged <5 years in 2015. LRTI episodes were categorized into moderate and severe episodes using standard definitions [33]. Disability per unit time for moderate and severe cases was 0.051 and 0.133, respectively [29]. Our analysis supplemented these data using additional prevalence and incidence data [28] (Supplementary Materials 4).

Modeling Studies
Yount and Mahle [27] performed a cost-utility analysis of RSV prophylaxis with palivizumab versus no intervention in a hypothetical group of 10 000 infants 6–7 months chronological age born premature and with congenital heart disease (CHD). Among the primary outcomes was cost per QALY saved. The primary source of utilities was a Canadian study of adults with congestive heart failure that evaluated health using time trade-off methods [30]. These values were extrapolated to the CHD population. The cost-utility analysis assumed a utility of 0.71 due to life-long exercise intolerance from preexisting CHD, a loss of 0.29 (Table 3). The baseline utility of the control group was assumed to be 1.0. QALYs lost per episode per child were not directly reported.

Elhassan et al [24] modeled the cost-benefit and cost-effectiveness of palivizumab prophylaxis in a hypothetical cohort of premature infants without chronic lung disease, accounting for risk of childhood asthma after RSV infection. The primary outcome measure in the analysis was QALYs. The QOL estimates for children with severe asthma was set at 0.89, and the absolute difference in QOL with and without asthma was provided (0.03). Health utility was assumed to be 1.0 for infants at baseline. These values were derived from previous studies of children aged 7–17 years using the Health Utility Index [31]. The change in QALYs was reported by gestational age, with the modeled difference between the palivizumab and no prophylaxis groups ranging from 0.0060 for infants born at 26 wGA to 0.0018 for infants born at 32 wGA (Table 3).

Similarly, Weiner et al [23] used a decision tree model simulating a cohort of Medicaid-insured infants aged 2.4 months with a history of prematurity (born at <35 wGA). The baseline utility in the group was assumed to be 1.0. Using the data from Leidy et al [21], Weiner et al incorporated utilities extrapolated from real-world estimates of parent proxies for their ill children and evaluated the immediate impact of RSV during and after hospitalization. The base case utility losses for hospitalization and for a 60-day postrecovery period were 0.3972 and 0.0911, respectively (Table 3). The change in QALYs ranged from 0.014 to 0.0539, based on extent of prematurity, chronological age at time of RSV, and risk factors.
0.0200 (Figure 2A). Both RSV cases and control groups consisted of infants or young children with a history of prematurity. The estimated incremental burden of RSV relative to prematurity alone for the child, caregiver, and family were 167%, 20%, and 77%, respectively, and for the child and caregiver dyad it was 78% (Figure 2B).

Figure 3 describes the QOL in cohort studies, showing both the control and RSV cohorts, and showing both the original data (Figure 3A) and cumulative effect (Figure 3B). The cumulative (solid) line in Figure 3B shows a steep rise in the first part of the illness, and a more moderate but constant rate of rise, in the second part of the illness. The slope (broken) line remains above zero, however, even in the second part of the illness. This result shows that the longer the period of follow-up of these premature infants with RSV, the greater the cumulative loss. Sensitivity analyses varying the QOL score on day 0, included in the Supplementary Materials 5–7, showed that this variation potentially changed the cumulative QOL loss at day 38 only minimally (by 0.4%).

**DISCUSSION**

Overall, this systematic literature review on the QOL of children with RSV revealed only 7 US studies published between 2000 and 2021. Our best estimate of the impact of an RSV LRTI episode on the child from direct observation was 0.0173 QALYs based on 2 pooled cohort studies in premature infants.

The continued lower QOL in RSV-infected infants compared with uninfected infants from days 38 through 60 suggests that there may be some additional difference, beyond the acute effect of the RSV episode, affecting QOL. Extrapolating the data...
from Leidy et al [21] we estimated a loss of 0.0169 QALYs to the infant during the acute episode and immediate recovery period for RSV. Several factors may explain the differences among the studies: (1) health utility modeling estimates that include losses from comorbidities that are not directly attributable to RSV; (2) evaluation of lifetime rather than short-term losses; and (3) a focus on loss of utilities in older children, adolescents, and adults rather than losses in infants and young children.

Validated tools for ascertaining QOL in infants and measuring infant health utilities are sparse. Although RSV is a common childhood disease, the existing studies are limited to children with preexisting health conditions, typically involving studies of children eligible for monoclonal antibodies for prophylaxis against the disease. Additionally, the early developmental level of young study participants presents a barrier to direct measurement of QOL, requiring researchers to rely on parent proxies.

The 4 modeling studies in this review illustrate the considerable challenges in assigning utility values for QOL in infants [23, 24, 26, 27]. The models assume a baseline utility of 1.0, representing the best health imaginable, despite evidence to the contrary in the matched control group [21]. The modeling studies using a lifetime perspective [23, 27] did not present the rationale for their utility assumptions. Both the modeling and the case-control studies focused on hospitalizations, excluding any evaluation of QOL in the outpatient setting and for non-medically attended RSV cases. Similarly, the emotional and physiologic impact of infant illness on a parent or caregiver was neglected in 3 of the 4 RSV studies. To overcome the dearth of information on RSV-associated QOL in the United States, data derived directly from a representative sample of term infants, young children, and their caregivers from both the inpatient and outpatient settings are needed.

The Infant Health-Related Quality of Life Instrument (IQI) is a recently developed tool consisting of 7 health items: sleeping, feeding, breathing, bowel function, mood, skin, and interaction. The initial study on the IQI used discrete choice experiments to derive health states; however, the values have yet to be standardized and organized into health utilities [34]. Once further validated, this tool has the potential to allow more accurate estimates of infant conditions and to evaluate the impact of interventions for this age group.

Table 4. Data Synthesis and Estimation of QALY Loss Due to an RSV Episode in Children, Caregivers, and Family Unit

| Measure^b | Child | Caregiver | Family |
|-----------|-------|-----------|--------|
| Average utility | 83.6 | 94.2 | 88.7 | 90.6 | 90.6 | 94.7 |
| Lost value (range, 0–100) | 16.5 | 5.8 | 11.3 | 9.4 | 9.4 | 5.3 |
| QALYs lost per day^d | 0.1645 | 0.0583 | 0.1132 | 0.0944 | 0.0939 | 0.0530 |
| Study period as fraction of a year | 0.1643 | 0.1643 | 0.1643 | 0.1643 | 0.1643 | 0.1643 |
| QALYs lost in RSV episode or control group in premature infants | 0.0270 | 0.0101 | 0.0186 | 0.0155 | 0.0154 | 0.0087 |
| QALYs lost in a year, less the effect of prematurity | 0.0169 | 0.0031 | 0.0067 |

Abbreviations: QALY, quality-adjusted life-year; RSV, respiratory syncytial virus.

^aBased on Leidy et al [21] alone because this was the only study to utilize the same scale (global rating of health) for the child and others.

^bAll groups were infants and children with a history of prematurity, gestational age at birth of ≤35 weeks.

^cOn the global rating of health scale with a maximum health value of 100.

^dTreating value as a utility.
The cumulative line in (cumulative loss was 0.0173 on day 38, the last time point with 2 QOL values. at a score of 90.9 and improved by 3.5 points by day 61. Using both studies, the be 52.4 in the RSV group and improved to 87.0 by day 66. The control group started
parative data (day 61). The extrapolated QOL score in (last common follow-up date between the 2 studies (day 38), and the end of com-
Labeled values (estimated QOL values) refer to the discharge date (day 6), the
or the newly developed IQI, the resulting combination of 12
items would measure disease-specific QOL and health utilities for estimating QALYs lost to illness.
Our systematic analysis has several limitations. Because of the heterogeneity of the modeling studies, we were able to uti-
ize only data from the 2 cohort studies to inform our estimates. Our data extraction had to rely on the graphs of means, point
estimates, and associated reported timelines from Leidy et al [21] and Pokrzywinski et al [22] to calculate utilities and QALYs. As there were no standard deviations or standard er-
ors of the mean report from these studies, we were unable to provide confidence intervals for our results. As the cohort stud-
ies only focused on very young children with a history of pre-
maturity, representing only a small percentage of children infected with RSV, the available data limit our ability to gener-
ze the results of utilities lost to RSV beyond these narrow groups.
In conclusion, published data on QOL of children in the United States with RSV are scarce and consider only premature hospitalized infants, whereas most RSV episodes occur in chil-
ren who were born at term and were otherwise healthy. To overcome this limitation, QOL studies are needed beyond hos-
pitalized premature infants. Finally, this study shows that the loss of QOL by other household members from a child’s RSV hospitalization adds appreciably to overall societal loss.

Supplementary Data
Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/).
Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes
Author contributions. E. L. G. contributed to protocol development and registration, search strategy development and data, data extraction, statistical and data analysis, review of results, manuscript development, review, and editing. D. H. contributed to data extraction, statistical and data analysis, review of results, manuscript development, review, and editing. K. R. R. and R. M. G. contributed to protocol development and registration, search strategy development and data, title and abstract review, full-text review, and data extraction. D. M. B. contributed to protocol development and registration, search strategy development and data, title and abstract review, full-text review, and data extraction. D. S. S. contributed to securing funding, protocol development and registration, search strategy development and data, data extraction, statistical and data analysis, review of results, manuscript development, review, and editing. L. B. contributed to protocol development and registration, search strategy development, and database

One measure developed specifically to evaluate the impact of influenza-like illness (ILI) on the parents of ill children is Care-ILI-QoL, a tool developed and validated in Australia, but with the potential for adaptation to other settings [35]. The Care-ILI-QoL survey consists of 17 items covering do-
 Figure 3. Quality of life in cohort studies. A. Pooling and analysis of the originally reported average QOL of the cohort studies combined [21, 22], and (B) cumulative QALY loss (solid line) and its slope (derivative, broken line). A, Symbols show dates for which each cohort contributed data (triangles denote control cohort, squares the Leidy et al RSV cohort [21], and circles the Pokrzywinski et al RSV cohort [22]). Labeled values (estimated QOL values) refer to the discharge date (day 6), the last common follow-up date between the 2 studies (day 38), and the end of comparative data (day 61). The extrapolated QOL score in (A) for day 0 was estimated to be 52.4 in the RSV group and improved to 87.0 by day 66. The control group started at a score of 90.9 and improved by 3.5 points by day 61. Using both studies, the cumulative loss was 0.0173 on day 38, the last time point with 2 QOL values. The cumulative line in (B) shows a steep rise in the first part of the episode, and a more moderate, but constant, rate of rise in the second part of the episode. The slope line remains above zero, however, even in the second part of the episode. This shows that the longer the period of follow-up of these premature infants with RSV, the greater the cumulative loss. It is possible that this pattern is a result of their prematurity and speaks to the need for RSV assessments in term infants. Abbreviations: QALY, quality-adjusted life-year; QOL, quality of life; RSV, respirato-
ry syncytial virus.
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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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