Received: 31 March 2023 | Revised: 28 May 2023 | Accepted: 31 May 2023

DOI: 10.1002/hsr2.1338

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Quality of life burden on United States infants and caregivers due to lower respiratory tract infection and adjusting for selective testing: Pilot prospective observational study

Dhwani Hariharan[1] | V. S. Senthil Kumar[1] | Elizabeth L Glaser[1] | William H. Crown[1] | Zachary A. Wolf[2] | Kimberley A. Fisher[3] | Charles T. Wood[3] | William F. Malcolm[3] | Christopher B. Nelson[4] | Donald S. Shepard[1]

[1]Heller School for Social Policy and Management, Brandeis University, Waltham, Massachusetts, USA

[2]Clinetic, Durham, North Carolina, USA

[3]Duke University School of Medicine, Duke University, Durham, North Carolina, USA

[4]Medical Evidence Generation, Sanofi, Swiftwater, Pennsylvania, USA

Correspondence

Donald S. Shepard, The Heller School for Social Policy and Management, Brandeis University, Waltham, MA 02454-9110, USA.
Email: shepard@brandeis.edu

Funding information

Sanofi; AstraZeneca

Abstract

Background and Aims: Policymakers need data about the burden of respiratory syncytial virus (RSV) lower respiratory tract infections (LRTI) among infants. This study estimates quality of life (QoL) for otherwise healthy term US infants with RSV-LRTI and their caregivers, previously limited to premature and hospitalized infants, and corrects for selective testing.

Methods: The study enrolled infants <1 year with a clinically diagnosed LRTI encounter between January and May 2021. Using an established 0–100 scale, the 36 infants' and caregivers' QoL at enrollment and quality-adjusted life year losses per 1000 LRTI episodes (quality-adjusted life years [QALYs]/1000) were validated and analyzed. Regression analyses examined predictors of RSV-testing and RSV-positivity, creating modeled positives.

Results: Mean QoL at enrollment in outpatient ($n = 11$) LRTI-tested infants (66.4) was lower than that in not-tested LRTI infants (79.6, $p = 0.096$). For outpatient LRTI infants ($n = 23$), median QALYs/1000 losses were 9.8 and 0.25 for their caregivers. RSV-positive outpatient LRTI infants ($n = 6$) had significantly milder QALYs/1000 losses (7.0) than other LRTI-tested infants ($n = 5$)(21.8, $p = 0.030$). Visits earlier in the year were more likely to be RSV-positive than later visits ($p = 0.023$). Modeled RSV-positivity (51.9%) was lower than the observed rate (55.0%). Infants' and caregivers' QALYs/1000 loss were positively correlated (rho = 0.34, $p = 0.046$), indicating that infants perceived as sicker imposed greater burdens on caregivers.

Conclusions: The overall median QALYs/1000 losses for LRTI (9.0) and RSV-LRTI (5.6) in US infants are substantial, with additional losses for their caregivers (0.25 and 0.20, respectively). These losses extend equally to outpatient episodes. This study is

Sanofi had the right to review but neither the decision to publish nor the contents of the manuscript were contingent on the sponsor's approval.

the first reporting QALY losses for infants with LRTI born at term or presenting in nonhospitalized settings, and their caregivers.

KEYWORDS

caregiver, lower respiratory tract infection, quality-adjusted life year (QALY), respiratory syncytial virus, RSV, quality of life

1 | INTRODUCTION

Lower respiratory tract infections (LRTI) are common among children under the age of 5 years; respiratory syncytial virus (RSV) is the most common viral pathogen. In the United States (US), RSV causes about 1.5 million outpatient visits, 500,000 emergency department (ED) visits and 57,527 hospitalizations among children under five annually with substantial burden in infants <1 year of age.[1] While healthcare utilization, including intensive care unit admission and use of mechanical ventilation, are important components of the economic burden due to RSV-LRTI,[2,3] other factors, such as caregiver stress and productivity loss,[4] and long-term complications,[5,6] also increase the overall economic burden of RSV.

Two observational studies[4,7] and one systematic analysis[8] have evaluated the extent of this impact on the health of the child and their caregiver in the United States. Both observational studies focused on infants with a history of prematurity.[4] The impact of RSV hospitalization on infants and caregivers' quality of life (QoL) was assessed using the Global Rating of Health scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). The systematic analysis found 16.9 quality-adjusted life years lost per 1000 episodes (QALY/1000) to the infant plus 3.1 QALY/1000 to the caregiver.[8] So far, cost-effectiveness analyses[9,10] have used such QoL estimates[7] when evaluating palivizumab, the existing prophylactic option for infants at higher risk of severe disease due to RSV-LRTI. Although prematurity and comorbidities are important risk factors for hospitalization, most hospitalized children (79%) with RSV were previously healthy.[11] A model of immunization of infants at low risk was limited to using healthcare events averted as outcomes due to the lack of QoL and QALY loss data in this population.[12] This study used a well-established numerical rating scale and caregiver surveys to generate QALY losses. These much needed results will permit future cost-effectiveness analyses to report costs per QALY gained, the recommended metric for economic evaluations in healthcare.[13,14]

A recent review identified the two multisetting studies reporting rates of RSV testing among LRTI cases.[15] The percentages of cases tested were highest in inpatients (83%–85%), followed by emergency department (ED) (29%) and outpatients (15%–25%).[16,17] Surveillance studies show that 97.1% of RSV episodes in children <2 years are nonhospitalized.[18,19] RSV testing outside of the inpatient setting is limited in the United States as the American Academy of Pediatrics does not recommend routine testing for RSV alone, mostly because pathogen identification generally would not affect clinical care.[20] Given the COVID-19 pandemic, clinicians may employ a respiratory panel including COVID-19 to determine the need for isolation. Hence, RSV testing is not random but is guided by the accessibility of testing, cost, and the usefulness of the information to clinical management.[15] Thus, identified positive cases understate the actual number of RSV cases, especially in the ED and outpatient settings, impeding policymakers' understanding of the etiology behind the illness and its prevalence in the population.

As its first main objective, this pilot prospective observational study estimated the overall loss in QoL and QALYs/1000 in medically-attended (MA) LRTI among infants <12 months of age and their caregivers. It extended across all clinical settings within the Duke University Health System (DUHS). The study's second objective was developing and piloting a method for a more precise estimate of the prevalence of RSV in a clinical setting and estimating observed and modeled QALY/1000 losses.

2 | METHODS

2.1 | Enrollment procedures

Infants aged 0–11 months and treated for LRTI within any DUHS facility (North Carolina, USA) between January 2021 and May 2021 were prescreened for eligibility in a cohort study.[21] Eligibility was based on clinical symptoms, ICD-10 codes and laboratory tests, applying World Health Organization criteria for RSV surveillance case definitions.[22] Eligible infants and their caregivers were invited to enroll in this prospective study entailing three phone interviews based on caregiver consent. Participating caregivers received $50 per completed interview.

2.2 | Questionnaire and administrative data

Infant and caregiver QoL were assessed using an established Global Rating of Health 0–100 scale, similar to prior studies,[4,7] with 0 indicating worst imaginable health and 100 indicating best-imaginable health. Appendix S1 illustrates the QoL component of the questionnaire at T0.

Caregivers provided household and infant characteristics, authorized access to the infant's medical record, and reported infants' health and their own health status before symptom onset (preonset), at enrollment (T0), and around 7 (T7) and 14 days (T14) later (Figure 1). The planned timeline had assumed that the first visit would

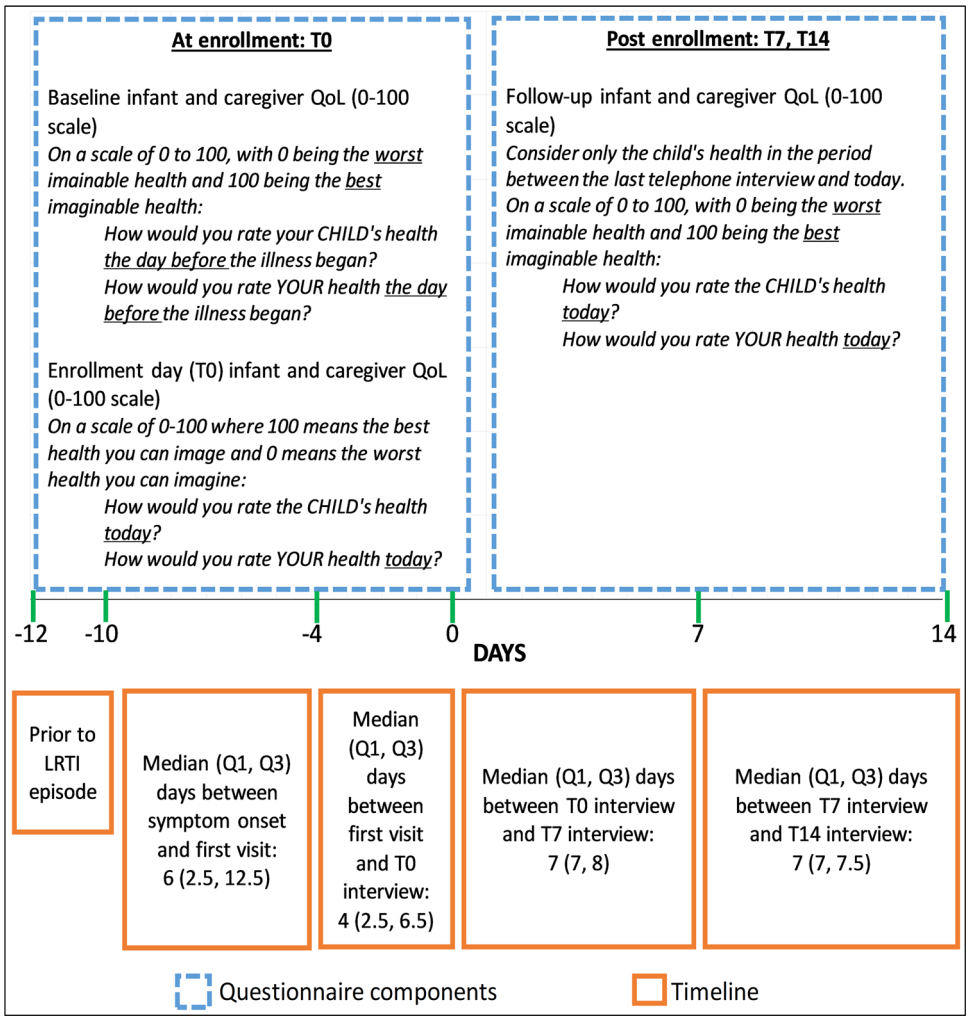

FIGURE 1 Observed interview timeline and quality of life questionnaire components. *Note*: QoL denotes quality of life; LRTI denotes lower respiratory tract infection; Q1 denotes first quartile (25th percentile); Q3 denotes third quartile (75th percentile); first visit denotes infant's earliest clinical encounter in the DUHS during the study period with LRTI diagnosis; T0 denotes enrollment interview following first visit; T7 denotes first post-enrollment follow-up interview; T14 denotes second postenrollment follow-up interview.

coincide with the first interview at T0. Due the time required to identify eligible infants and secure caregiver consent, however, the actual first interview was conducted 4 days (median) post first visit (Figure 1).

To cross-check the Global Rating of Health scale, the survey included the previously validated Care-ILI-QoL questionnaire.[23] The Care-ILI-QoL measures the QoL of caregivers of children with influenza-like illness (ILI) using a 7-point Likert scale (lowest values denote best health) with 17 items distributed over 4 domains. Additionally, the questionnaire included a 1–5 scale question on parental perception of infant health, with 1 being "*not sick at all*" and 5 being "*extremely sick*." The correlations between and across the two infant and two caregiver scales were assessed.

To minimize the time burden and privacy concerns on respondents, the survey did not collect data household demographics (e.g., number of other children), health of other children, nor socioeconomic characteristics. However, the linked administrative data did record the setting and payer for the care episode. Only low-income persons were eligible for Medicaid, so Medicaid payment signaled a low-income household.

2.3 | Estimating QALY loss

The calculation of QALY loss for the LRTI episode followed generic procedures,[24] a systematic analysis of RSV[8] and another viral illness.[25] The loss assessment (100 minus QoL score) was calculated at four time points (preonset, T0, T7, and T14). Based on the dates of those assessments, a piecewise linear function was fitted and the area under the curve (the sum of these trapezoidal areas as days of good health lost) was derived. The result was divided by 365 and then by 100 (the range of the 0–100 scale) to convert the value into an annual utility loss per case. To avoid confusion from small decimal values, QALY losses per case were multiplied by 1000 to express them as QALY/1000.

2.4 | Statistical analyses

Enrollees were classified according to their most intensive healthcare setting used (outpatient [including telemedicine ($n = 2$)]) only, ED only, and inpatient). Infants' and caregivers' QoL were analyzed by time points, RSV-testing status (tested vs. not tested) and testing results (RSV-positive vs. RSV-negative). QALY/1000 loss was analyzed by setting and payer (Medicaid vs. non-Medicaid). Distributions were tested for normality with Kolmogorov-Smirnov and Shapiro–Wilk tests.[26,27] Quality of life scores passed at least one of the two tests for normality and are presented as means, whereas QALY/1000 results failed both normality tests and are presented as medians. Variables were analyzed with two-sided independent *t*-test, Chi-square, Wilcoxon matched-pairs signed-rank and two-sample Wilcoxon rank-sum (Mann–Whitney *U*) tests using STATA 17.0[28] and Microsoft® Excel (Version 2112)[29] at the 5-percent significance levels unless otherwise stated. As the study sought to provide broader insights on the health impact of LRTI and RSV, the data were analyzed as a sample of a past, present and future flow of patients with LRTI treated in the DUHS.

2.5 | Adjusting for sample selection in LRTI testing

The predicted probability of an infant in the DUHS testing RSV-positive in the pilot data was estimated using predictors guided by available data, theory, past research, and clinical insights. "Treatment lag" is the number of days between caregiver's perception of LRTI symptom onset and the first visit for that LRTI. The variables analyzed using logistic regression included timing of index visit (measured as days since January 1, 2021), infant age (months) at enrollment, caregiver's estimate of infant's QoL at T0, the treatment lag, the highest care setting (outpatient, ED, or inpatient), and risk of hospitalization based on infant age.[30] The predicted positivity rate for infants not tested was estimated as a function of the statistically significant variable(s). Data for this study included complete results for RSV testing and positivity but only limited data about other pathogens (e.g., COVID-19 or influenza). Regression estimates could therefore not examine possible testing or confirmation of co-infections as possible predictors.

2.6 | Modeled RSV-positive and RSV-negative cases

Using the predicted probability of testing RSV-positive based on the results of regression analysis, the enrolled infants not tested for RSV were categorized into predicted-RSV-positive and predicted-RSV-negative groups and combined with the corresponding actually-tested observed-RSV-positive and observed-RSV-negative infants. Calculations using means used the entire sample in the corresponding setting and calculated weighted means, where the positive probability served as the weight for modeled-positive (observed and predicted) and the negative probability served as the weight for modeled-negative. Calculations based on medians classified an infant as modeled-RSV-positive if the predicted probability was 0.5 and above and modeled-RSV-negative otherwise.

2.7 | Ethics approval and consent

The study was approved by the DUHS Institutional Review Board on March 3, 2020 (IRB #Pro00104708). Informed consent was obtained from parents or legal guardians for all infants and caregivers included in the study.

3 | RESULTS

3.1 | Enrollees

Based on the inclusion criteria, 77 infants were eligible. Of those, 10 caregivers actively declined participation, 27 could not be reached, 2 were not English-speakers, 1 infant died, and 1 withdrew, resulting in 36 infants being enrolled. Nevertheless, enrollment rates did not vary significantly by payer, age, or setting but trended lower for outpatients (40%) and telemedicine (40%) compared to ED (67%) and inpatient (64%) settings ($p = 0.16$, Appendix S2). Overall, enrolled infants had an average (±standard error of the mean [SEM]) gestational age of 38.2 ± 0.5 weeks and an average chronological age of 7.2 ± 0.5 months at the index LRTI encounter (Table 1). As expected,[31] infants' chronological age varied significantly by LRTI-testing status (tested: 6.2 ± 0.8 months vs. untested: 8.5 ± 0.7 months, $p = 0.03$), although this difference was not as pronounced within each setting. RSV-positive infants were on average older than RSV-negative infants (7.6 ± 1.1 vs. 6.8 ± 0.7 months, respectively). Index RSV-LRTI encounters occurred significantly sooner after January 1, 2021, than non-RSV-LRTI encounters (69.9 ± 6.9 days vs. 100.4 ± 7.8, $p = 0.009$) (Table 1). Similar trends were observed in the outpatient and ED settings (Table 2).

For all enrolled infants, household income averaged (±SEM) $63,672 ± $6001. Household size (including the infant and caregiver) averaged 3.7 ± 0.2 members. About 50% of caregivers had an associate degree or higher level of education (Appendix S3).

3.2 | Quality of life results

Mean QoL among all LRTI infants at T0, regardless of testing status (75.0 ± 3.0), was significantly lower than their preonset level (90.8 ± 2.3), representing a 15.9 ± 3.2 decline ($p < 0.0001$). Overall, infants' QoL approached their preonset QoL by T7 (88.9 ± 2.3) and improved by T14 (91.0 ± 1.7) (Figure 2 and Appendix S4). Caregivers' QoL followed a similar pattern (Figure 2 and Appendix S5). Preonset QoL was below 100 (best imaginable) for 18/36 (50.0%) of infants and 15/36 (42%) of caregivers. Mean caregiver QoL was 89.6 ± 3.0

TABLE 1 Characteristics of all enrolled infants with LRTI by testing status.

Parameter	LRTI-not tested for RSV	LRTI-tested for RSV	RSV-LRTI-tested (observed)		RSV-LRTI modeled (observed and predicted)[a]		LRTI All
			RSV negative	RSV positive	RSV negative	RSV positive	
N (row %)	16 (44.4%)	20 (55.6%)	9 (25.0%)	11 (30.6%)	17.3 (48.1%)	18.7 (51.9%)	36 (100.0%)
Chronological age of infant (mean months ± SEM)[b]	8.5 ± 0.7	6.2 ± 0.8	5.8 ± 1.0	6.5 ± 1.1	6.8 ± 0.7	7.6 ± 0.8	7.2 ± 0.5
(*SD*)	(2.7)	(3.4)	(3.1)	(3.8)	(3.1)	(3.4)	(3.2)
Gestational age of infant (weeks ± *SEM*)	38.4 ± 0.6	38.1 ± 0.7	37.4 ± 1.5	38.8 ± 0.4	37.6 ± 0.9	38.8 ± 0.3	38.2 ± 0.5
(*SD*)	(2.4)	(3.2)	(4.6)	(1.5)	(3.7)	(1.5)	(2.9)
Days since Jan 1, 2021 to first visit (mean days ± SEM)[c]	88.6 ± 7.8	83.7 ± 6.1	100.4 ± 7.8	69.9 ± 6.9	102.7 ± 5.1	70.2 ± 6.0	85.9 ± 4.8
(*SD*)	(31.2)	(27.3)	(23.3)	(22.8)	(21.3)	(25.8)	(28.8)
Infants not recovered at T14 (*N*, col. %)[d]	5 (31.3%)	7 (35.0%)	4 (44.4%)	3 (27.3%)	6.5 (37.4%)	5.5 (29.5%)	12 (33.3%)
Caregivers not recovered at T14 (*N*, col. %)[d]	3 (18.8%)	7 (35.0%)	4 (44.4%)	3 (27.3%)	5.6 (32.6%)	4.4 (23.3%)	10 (27.8%)

Note: col. = column; N = number; % = percent.

Abbreviations: LRTI, lower respiratory tract infections; RSV denotes respiratory syncytial virus; SD, standard deviation; SEM, standard error of the mean.

[a]If probability of RSV positive ≥0.50, then classified as modeled positive; otherwise classified as modeled negative. All values are weighted by estimated RSV probability in the modeled category.

[b]Younger infants are more likely to be tested (*t*-statistic = −2.204, $p = 0.034$).

[c]RSV-positive infants are more likely to have a first LRTI visit earlier in the year relative to RSV-negative infants (*t*-statistic = −2.947, $p = 0.009$).

[d]QoL not returned to pre-infection baseline, i.e., T14 QoL < preonset QoL.

TABLE 2 Characteristics of enrolled infants with LRTI by testing status and setting.

Parameter	LRTI-not tested for RSV	LRTI-tested for RSV	RSV-LRTI tested (observed)		RSV-LRTI modeled (observed and predicted)[a]		LRTI All
			RSV negative	RSV positive	Modeled RSV negative	Modeled RSV positive	
Outpatient							
N (row %)	12 (52.2%)	11 (47.8%)	5 (21.7%)	6 (26.1%)	11.2 (48.7%)	11.8 (51.3%)	23 (100.0%)
Chronological age of infant (mean months ± SEM)[b]	8.2 ± 0.9	6.1 ± 1.0	5.8 ± 1.3	6.3 ± 1.6	6.8 + 0.9	7.6 + 1.0	7.2 ± 0.7
Gestational age of infant (mean weeks ± SEM)	38.2 ± 0.8	39.1 ± 0.5	39.8 ± 0.4	38.5 ± 0.7	38.6 ± 0.8	38.6 ± 0.5	38.6 ± 0.5
Days since January 1, 2021 to first visit (mean days ± SEM)[c]	87.8 ± 9.4	75.3 ± 7.8	90.2 ± 12.1	63.0 ± 7.7	98.2 + 6.9	66.2 + 7.7	81.8 ± 6.2
Infants not recovered at T14 (*N*, col. %)[d]	5 (41.7%)	4 (36.4%)	3 (60.0%)	1 (16.7%)	5.5 (48.9%)	3.5 (29.9%)	9 (39.1%)
Caregivers not recovered at T14 (*N*, col. %)[d]	2 (16.7%)	4 (36.4%)	2 (40.0%)	2 (33.3%)	3.4 (30.6%)	2.6 (21.8%)	6 (26.1%)
Emergency department							
N (row %)	2 (33.3%)	4 (66.7%)	1 (16.7%)	3 (50.0%)	2.1 (35.0%)	3.9 (65.0%)	6 (100.0%)
Chronological age of infant (mean months ± SEM)[e]	9.9 ± 0.8	5.9 ± 2.3	2.1 ± n.a.	7.2 ± 2.8	5.9 ± 3.1	8.0 ± 2.1	7.2 ± 1.7
Gestational age of infant (weeks ± SEM)	38.9 ± 1.9	38.9 ± 0.6	39.0 ± n.a.	38.8 ± 0.9	38.4 ± 1.1	39.2 ± 0.8	38.9 ± 0.6
Days since January 1, 2021 to first visit (mean days ± SEM)[f]	94.5 ± 29.5	75.3 ± 16.3	124.0 ± n.a.	59.0 ± 1.7	117.8 ± 15.3	62.4 ± 6.8	81.7 ± 13.4
Infants not recovered at T14 (*N*, col. %)[d]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Caregivers not recovered at T14 (*N*, col. %)[d]	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.2 (10.5%)	0.8 (20.0%)	1 (16.7.0%)
Inpatient							
N (row %)	2 (28.6%)	5 (71.4%)	3 (42.9%)	2 (28.6%)	4.0 (57.1%)	3.0 (42.9%)	7 (100.0%)
Chronological age of infant (mean months ± SEM)[g]	8.9 ± 1.3	6.6 ± 1.4	7.1 ± 2.1	5.9 ± 2.5	7.3 ± 1.5	7.2 ± 1.8	7.3 ± 1.1
Gestational age of infant (weeks ± SEM)	38.6 ± 0.6	35.5 ± 2.5	32.8 ± 3.4	39.7 ± 0.4	34.3 ± 2.8	39.2 ± 0.5	36.4 ± 1.8
Days since January 1, 2021 to first visit (mean days ± SEM)[h]	87.5 ± 23.5	108.6 ± 2.0	109.7 ± 3.4	107.0 ± 1.0	107.5 ± 6.2	96.1 ± 12.8	102.6 ± 6.6
Infants not recovered at T14 (*N*, col. %)[d]	0 (0.0%)	3 (60.0%)	1 (33.3%)	2 (100.0%)	1 (25.0%)	2 (66.7%)	3 (42.9%)
Caregivers not recovered at T14 (*N*, col. %)[d]	0 (0.0%)	3 (60.0%)	2(66.7%)	1(50.0%)	2 (50.0%)	1 (33.3%)	3 (42.9%)

Note: col. = column; N = number; % = percent; n.a. = not applicable (no SEM exists for a sample of 1).

Abbreviations: LRTI, lower respiratory tract infection; RSV denotes respiratory syncytial virus; SEM denotes standard error of the mean.

[a]If probability of RSV positive >0.50, then classified as modeled positive; otherwise classified as modeled negative. All values are weighted by estimated RSV probability in the modeled category.

[b]In the outpatient setting, there are no statistically significant differences in testing by chronological age of the infant (t-statistic = −1.5738, p = 0.1304).

[c]In the outpatient setting, RSV-positive infants are slightly more likely to have a first LRTI visit earlier in the year relative to RSV-negative infants (t-statistic = −1.963, p = 0.081).

[d]QoL not returned to pre-infection baseline, i.e., T14 QoL < preonset QoL.

[e]In the ED setting, there are no statistically significant differences in testing by chronological age of the infant (t-statistic = 1.135, p = 0.320).

[f]Differences in first LRTI visit relative to Jan 1, 2021 could not be tested in the ED setting due to small sample size.

[g]In the inpatient setting, there are no statistically significant differences in testing by chronological age of the infant (t-statistic = 0.932, p = 0.394).

[h]In the inpatient setting, there are no statistically significant differences between RSV-positive and RSV-negative infants by visit dates relative to Jan 1, 2021 (t-statistic = 0.602, p = 0.590).

preonset and decreased to 82.5 ± 3.3, although the reduction was not statistically significant ($p = 0.11$), before improving to preonset levels (T7: 89.9 ± 2.2, T14: 90.8 ± 2.5).

Among settings, outpatient infants and inpatient caregivers showed the largest decreases in mean QoL from preonset to enrollment (preonset: 90.9 ± 3.1; T0: 73.3 ± 4.0, $p = 0.0003$, and preonset: 94.3 ± 3.5; T0: 70.0 ± 10.4, $p = 0.085$, borderline significant, respectively) (Figure 3 and Appendices S4–S5).

There were no consistent differences in QoL between infants insured by Medicaid and those without-Medicaid. Across the 4 time periods and 3 modeled RSV categories (negative, positive, and overall), infants insured by Medicaid had higher QoL in 75% of the 12 combinations (Appendix S6). In the parallel comparison of the caregivers of these infants, those insured by Medicaid had higher QoL in 58% of the 12 combinations (Appendix S7).

The QoL scores on the 0–100 scale were negatively correlated, as expected, with the results on the corresponding 1–5 scale for infants and 1–7 Care-ILI-QoL scale for the caregivers at preonset, T0, T7, and T14. The two scales work in opposite directions. For the infant scales, the results were negatively correlated at T0 (Pearson coefficient = −0.2230, $p = 0.1912$) with significant associations at T7 (Pearson coefficient = −0.4397, $p = 0.007$) and T14 (Pearson coefficient = −0.5615, $p = 0.0004$). Among caregivers, except at T7, correlations between the 0–100 and interval scales at all time points were negative and significant (Appendix S8). Positive and significant correlations were expected for infant versus caregiver scale comparisons at all time points since the scales work in the same direction. Among all possible combinations, results on the 0–100 scale for infants versus caregivers showed the highest correlations (Appendix S9).

3.3 | RSV testing

The rates of RSV testing were 48% (11/23) in outpatient, 67% (4/6) in ED, 71% (5/7) inpatient, and 56% (20/36) in overall episodes. While variations in testing rates were consistent with previous research, our differences were not statistically significant ($p = 0.46$). RSV-tested infants consistently had lower mean QoL at enrollment compared to infants not tested in each setting. In the outpatient setting, 11/23 (48%) of the infants were RSV-tested and had lower mean QoL at enrollment (66.4 ± 5.3) than those not tested (79.6 ± 5.4, $p = 0.096$, borderline significant) (Appendix S4). Overall, caregivers of tested infants also had lower mean QoL at enrollment compared to caregivers of infants not tested, although not statistically significant (tested: 79.9 ± 5.1 vs. not-tested: 85.8 ± 3.8, $p = 0.381$) and did not improve to preonset levels (95.5 ± 2.1) by T14 (89.4 ± 3.3) (Appendix S5).

Among tested infants, RSV-negative infants appeared sicker than RSV-positive infants at all major time points (Figure 2). The preonset-to-enrollment decrement in mean QoL was particularly pronounced in the outpatient setting for RSV-negative infants (pre-onset:89.0 ± 9.8, T0:59.0 ± 9.9) (Figure 3 and Appendix S4). Caregivers showed similar patterns overall and by testing results (Figure 2 and Appendix S5).

3.4 | QALY/1000 loss

The overall estimated median QALY/1000 losses in infants with probable LRTI and their caregivers (LRTI-All) were 9.0 and 0.25, respectively. Expressed as QALY loss (rather than QALY/1000 loss) this median loss was 9.0×10^{-3} per infant. Median duration and QALY/1000 loss were greater in outpatient and ED infants than inpatients. Among tested infants, RSV-negative infants had a significantly worse QALY/1000 loss than RSV-positive cases (there was no information on testing data for other pathogens). The pattern was especially pronounced among outpatients (Table 3 and Appendix S10).

The caregiver's QoL at each time point and QALY were significantly associated with the infant's loss. Similar to a recent review,[8] this study shows that a LRTI episode affects the caregiver. Infants' and caregivers' overall QALY/1000 were significantly correlated (Spearman's rho = 0.34, $p = 0.046$) (Appendix S11).

3.5 | Predicted positivity rate

Among all predictors tested, the number of days from January 1, 2021 until the index visit was the only variable with a significant relationship with results of RSV testing and positivity in this pilot dataset (coefficient = −0.053, $p = 0.023$) (Appendix S12). As indicated by the negative coefficient, each additional day was associated with a lower likelihood of RSV-positivity, if tested. The variable had a range of 26–124 days with a mean of 85.8 days, meaning that the observations came from the end of the typical 2020–21 RSV season.

The predicted positivity rate averaged 55.0% among the tested infants, which agreed with the observed average (11/20). The mean days since January 1, 2021, was 88.6 days in all infants not tested and 83.7 days in tested infants. The average predicted positivity rates by subgroup were 48.1% in those not tested, 55.0% (as noted) in those tested, and 51.9% overall (Table 4).

3.6 | QoL and QALY/1000 loss among modeled positive and negative RSV cases

Using the predicted positivity rate of 48.6%, there were 7.7/16 predicted-RSV-positive LRTI cases and 8.3/16 predicted-RSV-negative cases among LRTI infants not tested for RSV. The total modeled-RSV-positive and modeled-RSV-negative cases, including both observed and predicted cases, were 18.7 and 17.3, respectively (Table 3 and Appendix S10). Relative to the observed-RSV-positive infants, the modeled cases appear to have lower QoL at each time point except T0. This result holds true across all settings except the inpatient setting, where the modeled-RSV-positive cases have better QoL compared to observed-RSV-positive cases at T0, T7, and T14 (Appendix S4). Caregiver QoL shows similar patterns among the modeled-RSV-positive and modeled-RSV-negative groups (Appendix S5).

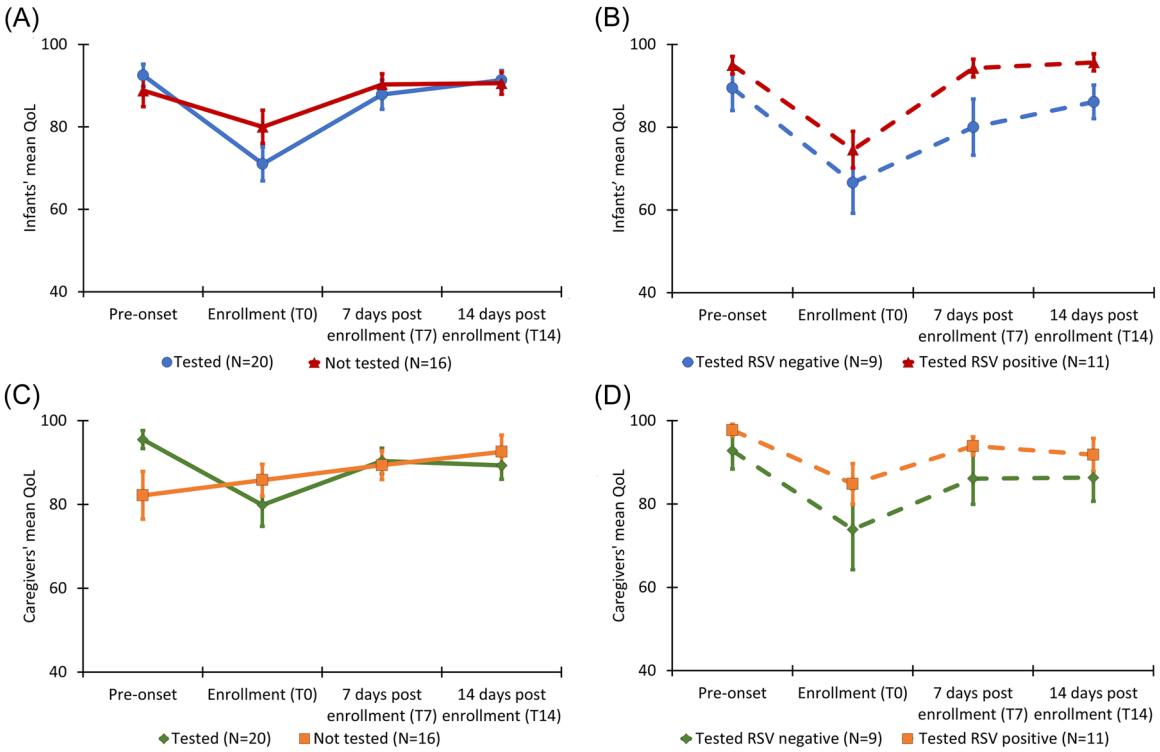

FIGURE 2 All infants ($N = 36$): mean infant and caregiver QoL on a 0–100 scale by status of RSV testing (A, C) and observed RSV positivity (B, D) of infants treated in all settings. *Note*: (for Figures 2 and 3): QoL denotes quality of life; RSV denotes respiratory syncytial virus; scale: 0 = worst imaginable health, 100 = best imaginable health; error bars represent standard deviations. All panels refer to infants treated in all settings. (A) Presents mean infant QoL at 4 time points among infants tested for RSV versus infants not tested for RSV at enrollment. (B) Presents mean infant QoL at 4 points among tested infants comparing RSV-negative and RSV-positive infants. (C) Presents mean QoL among caregivers of enrolled infants at 4 time points comparing caregiver QoL of RSV-tested vs RSV-not tested infants. (D) Presents mean QoL among caregivers of infants tested for RSV comparing caregiver QoL of RSV-negative and RSV-positive infants. QoL, quality of life; RSV, respiratory syncytial virus.

QALY/1000 loss among modeled-RSV-positive infants appears to either be similar or milder compared to observed-RSV-positive infants. Among modeled-RSV-negative infants, QALY/1000 loss is consistently worse overall and across settings. Differences between modeled-RSV-positive and modeled-RSV-negative QALY/1000 were smaller compared to the differences between observed-RSV-positive and observed-RSV-negative cases, although the modeled-RSV-positive cases continued to have milder QALY/1000 losses compared to modeled-RSV-negative cases. QALY/1000 loss among caregivers of modeled-RSV-negative infants was generally worse than that among caregivers of modeled-RSV-positive infants, except in the ED setting (Table 3 and Appendix S10).

4 | DISCUSSION

While previous studies in the United States have assessed QoL loss among hospitalized premature infants and their caregivers,[4,7] this pilot prospective observational study included otherwise healthy term infants across all clinical settings, including outpatients. This study found a median QALY/1000 loss of 9.0 (interquartile range [IQR]: 5.1–19.4) across all settings and gestational ages for an infant with an LRTI episode. Among inpatient modeled-RSV-positive LRTI infants, the median QALY/1000 loss was 5.5 (IQR: 4.6, 20.1). It is notable that this median value is substantially lower than the corresponding loss estimated in a systematic review in RSV-hospitalized infants who were also premature (16.9).[8] This comparison suggests that prematurity may magnify the burden of RSV. In addition to its innovation of including patients outside the inpatient setting, strengths of this study are the breadth and representativeness of the participants. Enrollees came from both hospital and outpatient sites of the DUHS. This network serves the majority of patients in its immediate catchment area. Enrollees were representative of all eligible patients on payer, age, or setting.

To our knowledge, this is the first United States study and only the second global study to examine QALY loss in nonhospitalized children with RSV. The one previous study of QALY loss in such children was based in the United Kingdom (UK).[32] Our median QALY/1000 loss of 9.0 is more than twice that of the average (3.8) for children receiving medical care in the UK study. However, while the UK study included children under 5 years, our study enrolled only children under 1 year. Our greater QALY loss is consistent with the

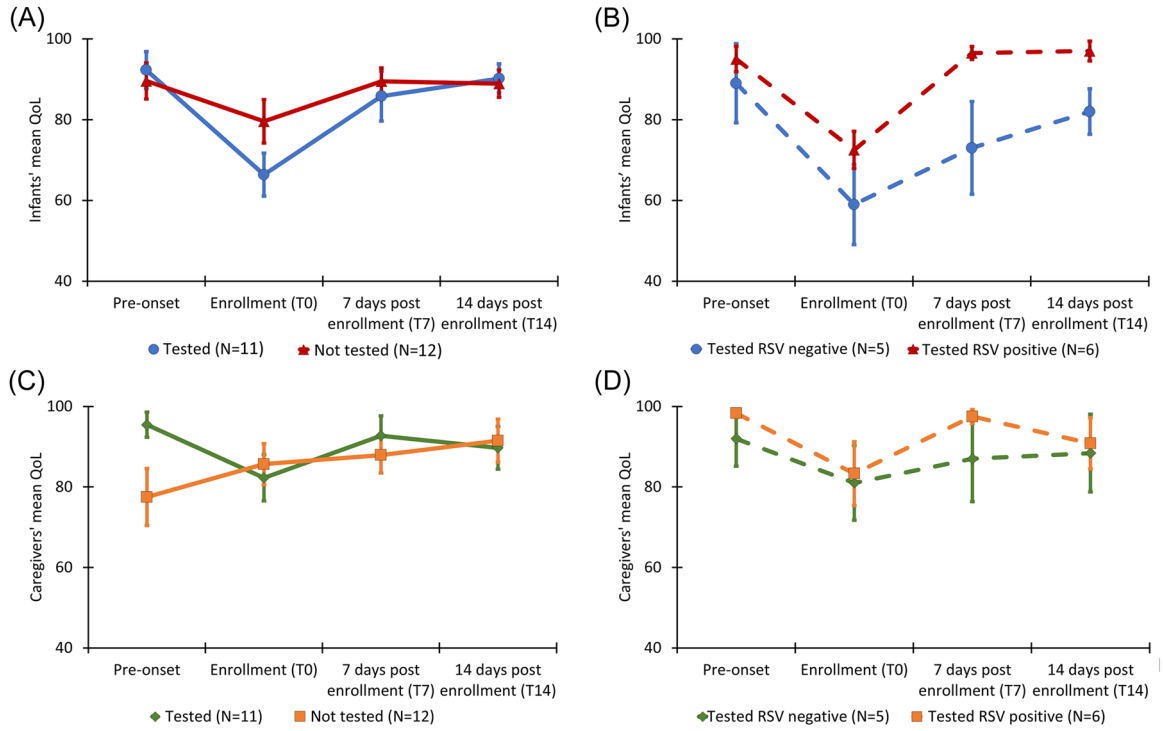

FIGURE 3 Outpatient infants ($N = 23$): mean infant and caregiver QoL on a 0–100 scale by status of RSV testing (A, C) and observed RSV positivity (B, D) of infants treated only in the outpatient setting. *Note*: see Figure 2 notes. All panels refer to infants treated only in the outpatient setting. (A) presents mean infant QoL at 4 time points among infants tested for RSV versus infants not tested for RSV at enrollment. (B) presents mean infant QoL at 4 points among tested infants comparing RSV-negative and RSV-positive infants. (C) presents mean QoL among caregivers of enrolled infants at 4 time points comparing caregiver QoL of RSV-tested versus RSV-not tested infants. (D) presents mean QoL among caregivers of infants tested for RSV comparing caregiver QoL of RSV-negative and RSV-positive infants. QoL, quality of life; RSV, respiratory syncytial virus.

finding that the severity of RSV episodes diminishes with the child's age.[30,33]

Unexpectedly, nonhospitalized episodes (both ED and outpatient) had longer durations and in turn worse QALY/1000 losses than inpatient episodes. As the calculation of QALY/1000 losses depended on the duration of illness, delays in seeking care or wait times for visits would have increased the observed duration of illness in the nonhospitalized settings.

The significant drop in median caregiver QoL from preonset to T0, and the significant correlation between caregiver and infant QALY/1000 losses show that the caregiver also suffers an adverse impact from the infant's LRTI. The caregiver's QALY/1000 loss (0.25) was only a fraction of the infant's loss (9.0), a pattern qualitatively similar to the previous review (3.1 vs. 16.9, respectively).[8] The absence of any systematic difference in RSV burden between infants insured by Medicaid and other payers suggests that the burden of RSV extends across infants and their caregivers, in both low- and middle-income households.

Since the majority of infant LRTI episodes in this study and nationally are outpatient, the potential aggregate QALY loss from RSV across settings could be substantial. A Canadian study suggests the burden could be even greater. There, 77.8% of parents of young infants with a mean chronological age (±SEM) of 2.7 ± 2.5 months who were hospitalized for RSV reported work impairments.[34] Although this study did not collect the data to allow examination of the relationship between the infant's illness and that of other household members beyond the caregiver, a national study did find such a relationship. Households with a well-child visit reported higher rates of subsequent influenza-like illness than control households.[35]

While this study's rates of RSV testing were not significantly different from the existing literature,[15–17] this study added empirical evidence around clinician decisions on testing during the study period (early 2021, before inter-seasonal surges later that year). First, results showed that caregivers of LRTI infants tested for causal pathogens reported a lower QoL at the index encounter (T0) than caregivers of nontested infants in the same setting. Physicians' perceptions of infant's illness at first visit (ascertained retrospectively, 4 days later) were likely correlated with caregivers' perceptions at T0 and could have influenced the need to test.

Second, clinicians may have been more likely to test for causal pathogens to assess the presence of COVID-19. The lower the quality of life, the more likely the physician will want to intensity prevention (e.g., isolating the infant or more personal protective equipment) or treatment (e.g., hospitalization). Past medical history,

TABLE 3 Duration of episode and QALY/1000 loss from LRTI of enrolled infants and their caregivers by setting.

Measure	LRTI-not tested for RSV	LRTI-tested for RSV	RSV-LRTI-tested (observed)[a]			RSV-LRTI modeled (observed and predicted)[a]			LRTI All[a]	
			RSV negative	RSV positive	Note[b]	RSV negative[c]	RSV positive[c]	Note[b]		Note[b]
All settings										
N	16	20	9	11		18 [15.8]	18 [16.5]		36	
Median duration of episode (days) (Q1, Q3)	27.5 (23, 31.5)	28 (20.5, 32.5)	30 (22, 33)	25 (19, 32)		30 (23, 33)	25 (22, 30)		28 (22.5, 32.5)	
Median QALY/1000 loss for infant (Q1, Q3)	9.1 (4.4, 13.4)	8.8 (5.6, 20.9)	**21.8 (7.8, 23.4)***	6.3 (4.6, 13.7)	[1]	**12.7 (7.8, 22.5)***	5.6 (4.1, 13.7)	[9]	9.0 (5.1, 19.4)	
Median QALY/1000 loss for caregiver (Q1, Q3)	0.30 (0.13, 0.69)	0.23 (0.01, 0.5)	**0.32 (0.02, 0.68)**	0.18 (0.00, 0.47)	[2]	**0.32 (0.10, 0.78)**	0.20 (0.00, 0.47)	[10]	0.25 (0.04, 0.57)	
Outpatient only										
N	12	11.0	5	6		12 [10.2]	11 [9.9]		23	
Median duration of episode (days) (Q1, Q3)	28 (24, 32)	24 (18, 33)	32 (19, 33)	23.5 (18, 25)		30 (19, 34)	25 (22, 28)		27 (22, 33)	
Median QALY/1000 loss for infant (Q1, Q3)	9.6 (4.0, 16.1)	9.8 (6.3, 21.8)	**21.8 (14.8, 25.1)***	7.0 (5.6, 9.8)	[3]	**14.8 (11.1, 25.1)**	5.6 (4.1, 9.8)	[11]	**9.8 (5.6, 19.6)**	[17]
Median QALY/1000 loss for caregiver (Q1, Q3)	0.42 (0.05, 0.77)	0.22 (0.00, 0.32)	**0.22 (0.02, 0.32)**	0.19 (0.00, 0.25)	[4]	**0.32 (0.01, 0.88)**	0.24 (0.00, 0.62)	[12]	0.25 (0.01, 0.75)	[18]
ED only										
N	2	4	1	3		2 [1.9]	4 [3.8]		6	
Median duration of episode (days) (Q1, Q3)	29.5 (26.0, 33.0)	30 (28, 46)	60 (60, 60)	28 (28, 32)		60 (33, 60)	28 (28, 32)		30 (28, 33)	
Median QALY/1000 loss for infant (Q1, Q3)	12.1 (10.0, 14.2)	11.1 (1.4, 21.3)	**23.4 (23.4, 23.4)**	2.9 (0.0, 19.3)	[5]	**23.4 (10.0, 23.4)**	2.9 (0.0, 19.2)	[13]	**12.1 (2.9, 19.3)**	[17]
Median QALY/1000 loss for caregiver (Q1, Q3)	0.24 (0.20, 0.27)	0.04 (0.00, 0.27)	0.00 (0.00, 0.00)	**0.07 (0.00, 0.47)**	[6]	0.00 (0.00, 0.27)	**0.07 (0.00, 0.47)**	[14]	0.14 (0.00, 0.27)	[18]
Inpatient										
N	2	5	3	2		4 [3.8]	3 [2.8]		7	
Median duration of episode (days) (Q1, Q3)	21 (19, 23)	28 (22, 30)	28 (22, 30)	27 (19, 35)		28 (22, 30)	19 (19, 35)		23 (19, 30)	

TABLE 3 (Continued)

Measure	LRTI-not tested for RSV	LRTI-tested for RSV	RSV-LRTI-tested (observed)[a]			RSV-LRTI modeled (observed and predicted)[a]			LRTI All[a]	Note[b]
			RSV negative	RSV positive	Note[b]	RSV negative[c]	RSV positive[c]	Note[b]		
Median QALY/1000 loss for infant (Q1, Q3)	5.3 (4.6, 6.0)	7.8 (5.5, 20.1)	7.8 (3.8, 22.5)	**12.8 (5.5, 20.1)**	[7]	**7.8 (3.8, 22.5)**	5.5 (4.6, 20.1)	[15]	6.0 (4.6, 20.1)	[17]
Median QALY/1000 loss for caregiver (Q1, Q3)	0.18 (0.16, 0.21)	0.52 (0.41, 0.68)	**0.68 (0.41, 1.11)**	0.35 (0.18, 0.52)	[8]	**0.68 (0.41, 1.11)**	0.18 (0.16, 0.52)	[16]	**0.41 (0.18, 0.68)**	[18]

Note: LRTI QALY losses are expressed per 1000 episodes, where higher numbers represent worse health; Q1 denotes first quartile (25th percentile) and Q3 denotes third quartile (75th percentile); QALY loss and duration of episode values presented are weighted medians within the classified groups; statistical analyses used the two-sample Wilcoxon rank-sum (Mann–Whitney *U*) test and are based on unweighted observations.

Abbreviations: ED, emergency department; LRTI, lower respiratory tract infection; QALY, quality-adjusted life years; RSV, denotes respiratory syncytial virus.

[a]Results of statistical tests comparing QALY losses for infants and their caregivers are reported in Appendix S10. Bolded values indicate the larger QALY loss between RSV-positive and RSV-negative groups in a given row, and between settings across rows, and bolded values with asterisks indicate that the larger value is statistically significantly larger at the 5% level.

[b]Notes columns: For results of significance tests, refer to Appendix S10.

[c]Infants were assigned to the LRTI-presumed RSV positive group if predicted probability was ≥0.50 for statistical analysis. The sum of the predicted positivity or negativity weights are presented in parentheses next to the overall N's.

parental concern, infant age, and the clinician's judgment of disease severity may also affect testing. These findings are consistent with the results of the systematic literature review finding that 21% (6/28) of studies reported that a physician decision governed testing practices.[15] These observations can help researchers refine estimates of the total incidence of RSV-related illness.

While researchers are aware that RSV testing is selective, so numbers of reported cases are a lower bound on actual counts, the degree of underestimation is poorly understood. Using predictors of the decision to test can be a powerful tool. This study estimated a 51.9% overall prevalence of RSV in this clinical cohort based on predicted positivity rate. It is slightly below the observed rate in those tested for RSV (11/20 [55.0%]). This pattern was expected, as testing in this sample was more likely among infants who may be sicker or were tested for RSV as part of a respiratory panel to rule out COVID-19. By incorporating both observed and modeled RSV-positive infants, this study provides QoL scores and QALY/1000 losses adjusting for varying testing practices. By focusing on RSV-tested infants alone, overall QoL burden may be overestimated.

Modeled-RSV-positive infants consistently had smaller QALY/1000 losses across the settings relative to modeled-RSV-negative infants. Similarly, observed-RSV-positive infants had lower QALY/1000 losses compared to observed-RSV-negative infants. As RSV ranks as the leading cause of hospital admission in infants,[36] its second-tier status on severity may appear inconsistent. However, closer examination reconciles the findings. To interpret RSV's lower severity, it is helpful to recall that all infants in this study sought medical attention for an LRTI. That infection could have been due to RSV or some other cause. The fact that the QALY loss of the modeled RSV-positive infants was lower than that of the modeled RSV-negative cases means that the other causes of LRTI, such as pneumonia, caused even worse QALY losses than RSV. The leading cause ranking does not relate to severity, but is frequency based on diagnosis classifications. RSV hospitalizations count as a single category, whereas pneumonia hospitalizations are divided among multiple categories based on the pathogen responsible.

The method suggested in this study for selective testing parallels the work of James J. Heckman, who shared the Nobel Prize in economics in 2000 for contribution to methods for analyzing data from selective samples.[37,38] Such methods have been widely applied to evaluate medical and pharmacological interventions but not in testing literature.[39] Researchers often use regression analysis (as done here) or propensity-based scores to incorporate observed variables, and Heckman analyses to control for unobserved factors. In larger datasets, future studies might include multi-variable predictors of testing, with various transformations, as possible Heckman factors. These include access to telehealth consultation and distance (in miles or time) from the testing site. If clinicians tend to order testing where they expect the test result to be positive, correction for unmeasured characteristics would likely make the estimated RSV prevalence based on unobserved variables even lower than the rate corrected just for observed ones. Also, in data collected since 2020 patterns of

TABLE 4 Observed and predicted RSV-positivity rate overall and in the outpatient setting.

Group	Number of presumed RSV-positive LRTI infants	Number of presumed RSV-negative LRTI infants	Total	Modeled positivity rate[a]
Overall				
Tested (observed)	11.0	9.0	20.0	55.0%
Not tested (predicted only)	7.7	8.3	16.0	48.1%
Combined (total modeled)	18.7	17.3	36.0	51.9%
Outpatient				
Tested (observed)	6.0	5.0	11.0	54.5%
Not tested (predicted only)	5.7	6.3	12.0	47.9%
Combined (total modeled)	11.7	11.3	23.0	51.1%

Note: LRTI denotes lower respiratory tract infection; RSV denotes respiratory syncytial virus.

[a]The predicted positivity rate between those tested and not tested is not statistically different overall (z-score = 0.299, $p = 0.76$) and in outpatients (z-score = 0.218, $p = 0.83$).

seasonality and age-specific RSV risk may have changed due to non-pharmaceutical interventions.[40,41]

Extensions to these methods are presented in Appendix S13 where parametric sample selection bias models that incorporate inverse Mills ratio (IMR) are explained. These models provide a test for the presence of unobserved variables that could introduce bias in estimates of outcomes, such as QoL, associated with testing. Moreover, if such variables are found to be present, these models provide a correction for the bias. These corrections for selective testing are important to understand the true burden of RSV-LRTI, estimate unbiased QALY losses and assist immunization strategy recommendations.

The finding that LRTI infants who tested RSV-negative had lower QoL than who tested RSV-positive adds context to the burden of RSV. In the present study, confirmed RSV-LRTI constituted 31% (11/36) of all LRTI episodes and non-RSV LRTI had a lower QoL than RSV-LRTI. In a recent study, RSV-LRTI-related ICD-10 diagnoses constituted 9.3% of US infant hospital admissions (excluding births) from October 2015 through December 2019.[36] These results imply that 69% (100%–31%) of infant LRTI episodes and 90.7% (100.0%–9.3%) of infant non-birth hospitalizations are due to causes other than RSV-LRTI. Similarly, pneumonia caused about four times the number of infant deaths compared to RSV and bronchiolitis combined.[42–44] These findings indicate the potential value of systematic or random testing of all infants with LRTI to inform public health policies and the need to strengthen the prevention and management of all causes of infant illness.

Recent product and policy advances have increased the salience of this and potential follow-on studies. Clinical trials found that passive immunization of infants significantly reduced medically attended RSV[45] and maternal vaccination significantly lowered severe RSV in their infants.[46] In February 2023, the Advisory Committee on Immunization Practices[47] formally examined passive [immunization and in May 2023, an advisory panel to the US Food and Drug Administration recommended approval of that maternal vaccine.[48] Quantification of the QALY/1,000 losses to infants and caregivers can inform the potential public health benefits and cost-effectiveness of these products.

Conducting cohort studies similar to this one in other settings would increase policymakers' understanding of the burden of LRTI and RSV and strengthen procedures for adjusting for the selectivity of RSV testing. An ideal future study would be based in one or more health systems across geographically diverse and varied sites (inpatient, emergency room, and outpatient). Variation in provider attitudes and the availability of testing panels for viral illness would enrich the analysis of factors around the decision to test for RSV and the modeling of RSV positivity. Enrollment should begin before the expected start and continue at least through the end of the RSV season, and preferably for a full year. If possible, caregivers should be asked to enroll on the day of their initial visit to maximize their recall.

Several limitations of this work must be acknowledged. First, as 33% (12/36) of infants and 28% (10/36) of caregivers had not returned to their preonset QoL at T14 (the last measurement), this truncation in follow-up likely understated actual QALY burdens. Second, the data came from a single health system. As one of its hospitals was a referral hospital, the study population may have had a higher share of severe cases than a population-based sample. Third, the 5.0-day average lag between the index encounter and interview (median days = 4, Figure 1), due to time for arranging consent, probably introduced some measurement error. Fourth, given the study's focus on RSV, complete information on test results and diagnoses on infants not positive for RSV was not available for this study. Fifth, as a pilot during months of low RSV incidence, the study was based on a sample of only 36 infants and their caregivers. Sixth, patients were recruited during the COVID-19 pandemic when the expected 2020–21 RSV seasonal disease was disrupted and only sporadic infant LRTI cases were documented. During that year, inter-seasonal RSV LRTI occurred in July-September, 2021,[49] after enrollment had ended. Furthermore, the pandemic may have

influenced the results by altering healthcare utilization patterns (i.e., use of telemedicine vs ED, etc.) or may have impacted caregiver QoL in other ways, such as childcare difficulties or other financial and social burdens. As a result, these findings may need to be adapted to the changing epidemiology of RSV, such as the early onset in 2022 or a return to more typical RSV seasons.[50,51] Seventh, multiple comparisons could potentially have led to false positive results as the study had four measurement times and various subgroups. However, our focus on the main outcome (median QALYs/1000 lost for infants and their caregivers) and our small sample size mitigated this theoretical risk.

Finally, there are three questions about whether the sample size of 36 infants and their caregivers is sufficient for meaningful findings. The first question concerns the representativeness of the enrollees compared to eligible DUHS patients during the study period (January–May 2021). The 36 enrollees constitute 47% of the 77 eligible patients. Enrollment rates proved similar across the various major categories of payer, setting and age, indicating that the enrollees were representative of those eligible (Appendix S2). Indeed, the study could have limited the focus to the actual population of 47 patients diagnosed at DUHS with LRTI, rather than a sample of past and current patients. Under that more limited approach, the statistical analysis would have incorporated a finite population correction, reducing the standard deviation by 27%, making differences even more highly statistically significant.[52] However, the authors felt that considering the enrollees as a sample of both past and present patients generated a more generalizable and useful analysis.

The second question concerns the representativeness of enrollees compared to past patients. The similarity of current and past patients was demonstrated by a retrospective comparison between the 987 RSV or bronchiolitis encounters during the COVID-19 period (March 29, 2020 through October 30, 2021) against the 1595 pre-COVID-19 encounters (October 4, 2015 through March 28, 2020).[15] Except for timing, the distribution of episodes across settings were comparable, with all differences under 6 points. The third question concerns the statistical power of the study. The sample was sufficient to develop and demonstrate an approach to correcting for selective testing and to generate statistically significant findings for several key outcomes, such as the decrement in QoL from preonset to T0 ($p < 0.0001$).

5 | CONCLUSIONS

While previous research covered only hospitalized premature infants, this pilot study extended results to include nonhospitalized and term LRTI infants in the US. The overall burden of LRTI and RSV-LRTI on infants and their caregivers is substantial, particularly for full-term infants seeking care in outpatient settings. Infants with lower QoL were more likely to be tested in outpatient settings. Using predictive modeling, this study provided an approach to measure the overall QALY losses from RSV, even among infants not tested. As the Global Rating of Health required only a single question and provides valuable data on QoL and QALYs for infants and caregivers, it merits wider replication in clinical and surveillance studies.

AUTHOR CONTRIBUTIONS

Dhwani Hariharan: conceptualization; formal analysis; visualization; writing—original draft; writing—review & editing. **V. S. Senthil Kumar**: formal analysis. **Elizabeth L. Glaser**: conceptualization; formal analysis; writing—original draft. **William H. Crown**: Methodology; Writing—original draft; Writing—review & editing. **Zachary A. Wolf**: data curation; project administration. **Kimberley A. Fisher**: data curation; project administration; supervision. **Charles T. Wood**: data curation; Writing—review & editing. **William F. Malcolm**: data curation; writing—review & editing. **Christopher B. Nelson**: funding acquisition; supervision; writing—review & editing. **Donald S. Shepard**: conceptualization; formal analysis; funding acquisition; methodology; supervision; writing—original draft; writing—review & editing. All authors have read and approved the final version of the manuscript. Dr. Donald S. Shepard had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGMENTS

The authors thank participating caregivers for their time, Shannon Carr from Clinetic, Durham, NC, for coordinating data retrieval from the Duke University Health System, Heidi Reichert and Mina Suh from EpidStrategies, Ann Arbor, MI, for their assistance in data management, Diana M. Bowser and Clare L. Hurley from Brandeis University, Waltham, MA, for constructive comments and editorial assistance, respectively, and Maria Y Chow, University of Sydney and National Center for Immunization Research and Surveillance, for use of the Care-ILI-QoL (co-authored with JK Yin, L Heron, AM Morrow, A Dierig, R Booy and J Leask). This collaborative study among Brandeis University, Clinetic, and Duke University was funded by Sanofi and AstraZeneca.

CONFLICT OF INTEREST STATEMENT

Christopher B. Nelson is an employee of Sanofi and may hold shares and/or stock options in the company. All other authors received grant funding from Sanofi and AstraZeneca (through Sanofi). Kimberley A. Fisher, Charles T. Wood, William F. Malcolm received grant funding for this study from Sanofi and AstraZeneca through Clinetic. Donald S. Shepard has received financial support from Abbott, Inc, Takeda Vaccines, Inc. and Trustees of Columbia University, New York, in the past 36 months. Dhwani Hariharan, William H. Crown and V.S. Senthil Kumar have received financial support from Bill & Melinda Gates Foundation and The Global Fund to Fight AIDS, Tuberculosis and Malaria, in the past 36 months.

DATA AVAILABILITY STATEMENT

Address data requests to Clinetic, Durham, NC, attention Zachary Wolf, zwolf@clinetic.com.

ETHICS STATEMENT

The study was approved by the Duke University Health System Institutional Review Board on March 3, 2020 (IRB #Pro00104708). Informed consent was obtained from parents or legal guardians for all infants and caregivers included in the study. Caregivers of eligible infants were invited to enroll in this prospective study entailing three phone interviews. Informed consent was obtained from parents or legal guardians for all infants included in the study. Consenting caregivers received $50 per completed interview.

TRANSPARENCY STATEMENT

The lead author Donald S. Shepard affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Dhwani Hariharan http://orcid.org/0000-0001-7329-7376
V. S. Senthil Kumar https://orcid.org/0000-0002-7313-7943
Elizabeth L Glaser http://orcid.org/0000-0002-1918-057X
William H. Crown http://orcid.org/0000-0002-8822-2737
Zachary A. Wolf http://orcid.org/0000-0001-9840-4764
Kimberley A. Fisher http://orcid.org/0000-0003-0851-3401
Charles T. Wood http://orcid.org/0000-0002-6884-8265
William F. Malcolm http://orcid.org/0000-0001-7080-7625
Christopher B. Nelson http://orcid.org/0000-0003-1046-7635
Donald S. Shepard http://orcid.org/0000-0003-2187-0593

REFERENCES

1. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360(6):588-598. doi:10.1056/NEJMoa0804877
2. McLaurin KK, Farr AM, Wade SW, Diakun DR, Stewart DL. Respiratory syncytial virus hospitalization outcomes and costs of full-term and preterm infants. *J Perinatol*. 2016;36(11):990-996. doi:10.1038/jp.2016.113
3. Young M, Smitherman L. Socioeconomic impact of RSV hospitalization. *Infect Dis Ther*. 2021;10(suppl 1):35-45. doi:10.1007/s40121-020-00390-7
4. Pokrzywinski RM, Swett LL, Pannaraj PS, et al. Impact of respiratory syncytial virus-confirmed hospitalizations on caregivers of US preterm infants. *Clin Pediatr*. 2019;58:837-850. doi:10.1177/0009922819843639
5. Chirikov VV, Simões EAF, Kuznik A, Kwon Y, Botteman M. Economic-burden trajectories in commercially insured US infants with respiratory syncytial virus infection. *J Infect Dis*. 2019;221(8):1244-1255. doi:10.1093/infdis/jiz160
6. Simões EAF, Liu AH. RSV prevention in infancy and asthma in later life. *Lancet Respir Med*. 2018;6(7):e30. doi:10.1016/S2213-2600(18)30230-3
7. Leidy NK, Margolis MK, Marcin JP, et al. The impact of severe respiratory syncytial virus on the child, caregiver, and family during hospitalization and recovery. *Pediatrics*. 2005;115:1536-1546. doi:10.1542/peds.2004-1149
8. Glaser EL, Hariharan D, Bowser DM, et al. Impact of respiratory syncytial virus on child caregiver, and family quality of life in the United States: systematic literature review and analysis. *J Infect Dis*. 2022;226(suppl 2):S236-S245. doi:10.1093/infdis/jiac183
9. Mahadevia PJ, Masaquel AS, Polak MJ, Weiner LB. Cost utility of palivizumab prophylaxis among pre-term infants in the United States: a national policy perspective. *J Med Econ*. 2012;15(5):987-996. doi:10.3111/13696998.2012.690013
10. Weiner LB, Masaquel AS, Polak MJ, Mahadevia PJ. Cost-effectiveness analysis of palivizumab among pre-term infant populations covered by Medicaid in the United States. *J Med Econ*. 2012;15:997-1018. doi:10.3111/13696998.2012.672942
11. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics*. 2013;132(2):e341-e348. doi:10.1542/peds.2013-0303
12. Kieffer A, Beuvelet M, Sardesai A, et al. Expected impact of universal immunization with nirsevimab against RSV-related outcomes and costs among all US infants in their first RSV season: a static model. *J Infect Dis*. 2022;226(suppl 2):S282-S292. doi:10.1093/infdis/jiac216
13. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG, eds. *Cost-Effectiveness in Health and Medicine*. Second edition. Oxford University Press; 2016.
14. Weinstein MC. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA*. 1996;276(15):1253-1258. doi:10.1001/jama.1996.03540150055031
15. Movva N, Suh M, Bylsma LC, Fryzek JP, Nelson CB. Systematic literature review of respiratory syncytial virus laboratory testing practices and incidence in United States infants and children <5 years of age. *J Infect Dis*. 2022;226(suppl 2):213. doi:10.1093/infdis/jiac203
16. Flaherman V, Li S, Ragins A, Masaquel A, Kipnis P, Escobar GJ. Respiratory syncytial virus testing during bronchiolitis episodes of care in an integrated health care delivery system: a retrospective cohort study. *Clin Ther*. 2010;32(13):2220-2229. doi:10.1016/S0149-2918(10)80025-6
17. Turi KN, Wu P, Escobar GJ, et al. Prevalence of infant bronchiolitis-coded healthcare encounters attributable to RSV. *Health Sci Rep*. 2018;1(12):e91. doi:10.1002/hsr2.91
18. Lively JY, Curns AT, Weinberg GA, et al. Respiratory syncytial virus-associated outpatient visits among children younger than 24 months. *J Pediatric Infect Dis Soc*. 2019;8(3):284-286. doi:10.1093/jpids/piz011
19. Rha B, Curns AT, Lively JY, et al. Respiratory syncytial virus-associated hospitalizations among young children: 2015-2016. *Pediatrics*. 2020;146(1):e20193611. doi:10.1542/peds.2019-3611
20. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5):e1474-e1502. doi:10.1542/peds.2014-2742
21. Suh M, Reichert H, Movva N, et al. Pilot surveillance of infant lower respiratory tract infections and respiratory syncytial virus in the United States during the COVID pandemic. To be presented at: International Conference on Pharmacoepidemiology (ICPE); August 2023 Halifax, Nova Scotia, Canada (forthcoming).
22. World Health Organization. RSV surveillance case definitions. [cited: 24 Jan 2022]. https://www.who.int/teams/global-influenza-programme/global-respiratory-syncytial-virus-surveillance/case-definitions
23. Chow MYK, Yin JK, Heron L, et al. The impact of influenza-like illness in young children on their parents: a quality of life survey. *Qual Life Res*. 2014;23:1651-1660. doi:10.1007/s11136-013-0606-3
24. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL, eds. *Methods for the Economic Evaluation of Health Care Programmes*. Third Edition. Oxford University Press Inc.; 2005.

25. Zeng W, Halasa-Rappel YA, Durand L, Coudeville L, Shepard DS. Impact of a nonfatal dengue episode on disability-adjusted life years: a systematic analysis. *Am J Trop Med Hyg*. 2018;99(6):1458-1465. doi:10.4269/ajtmh.18-0309
26. Massey FJ. The Kolmogorov-Smirnov test for goodness of fit. *J Am Stat Assoc*. 1951;46(253):68-78. doi:10.2307/2280095
27. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). *Biometrika*. 1965;52(3/4):591-611. doi:10.2307/2333709
28. StataCorp. *Stata Statistical Software: Release 17, released April 2021*. StataCorp LLC; 2021.
29. Microsoft Corporation. Microsoft Excel, Version 2112 (Build 14729.20194) released Jan. 4, 2022. [cited: https://www.microsoft.com/en-us/microsoft-365/excel.
30. Shepard DS, Perloff J, Jiang X, et al. Impacts of age and season on rates of hospitalization for respiratory syncytial virus (RSV) in infants in the United States and their use of mechanical ventilation and charges (Session: Virology: studies of the epidemiology of viral infections, poster: 1708). Presented at ID Week, October 21 - 25, 2020. doi:10.1093/ofid/ofaa439.1886
31. Hodges EN, White M, Nelson CB. All infants are at risk of developing medically attended respiratory syncytial virus lower respiratory tract infection and deserve protection. *J Infect Dis*. 2022;226(suppl ment 2):S148-S153. doi:10.1093/infdis/jiac244
32. Hodgson D, Atkins KE, Baguelin M, et al. Estimates for quality of life loss due to respiratory syncytial virus. *Influenza Other Respir Viruses*. 2020;14(1):19-27. doi:10.1111/irv.12686
33. Bowser DM, Rowlands KR, Hariharan D, et al. Cost of respiratory syncytial virus infections in US infants: systematic literature review and analysis. *J Infect Dis*. 2022;226(suppl ment 2):S225-S235. doi:10.1093/infdis/jiac172
34. Mitchell I, Defoy I, Grubb E. Burden of respiratory syncytial virus hospitalizations in Canada. *Can Respir J*. 2017;2017:e4521302. doi:10.1155/2017/4521302
35. Simmering JE, Polgreen LA, Cavanaugh JE, Polgreen PM. Are well-child visits a risk factor for subsequent influenza-like illness visits? *Infect Control Hosp Epidemiol*. 2014;35(3):251-256. doi:10.1086/675281
36. Suh M, Movva N, Jiang X, et al. Respiratory syncytial virus is the leading cause of United States infant hospitalizations, 2009–2019: a study of the national (nationwide) inpatient sample. *J Infect Dis*. 2022;226(suppl ment 2):S154-S163. doi:10.1093/infdis/jiac120
37. Heckman JJ. Sample selection bias as a specification error. *Econometrica*. 1979;47(1):153-161. doi:10.2307/1912352
38. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55. doi:10.1093/biomet/70.1.41
39. Crown WH. Propensity-score matching in economic analyses: comparison with regression models, instrumental variables, residual inclusion, differences-in-differences, and decomposition methods. *Appl Health Econ Health Policy*. 2014;12(1):7-18. doi:10.1007/s40258-013-0075-4
40. Li Y, Wang X, Cong B, Deng S, Feikin DR, Nair H. Understanding the potential drivers for respiratory syncytial virus rebound during the coronavirus disease 2019 pandemic. *J Infect Dis*. 2022;225(3):957-964. doi:10.1093/infdis/jiab606
41. Zheng Z, Pitzer VE, Shapiro ED, Bont LJ, Weinberger DM. Estimation of the timing and intensity of reemergence of respiratory syncytial virus following the COVID-19 pandemic in the US. *JAMA Network Open*. 2021;4(12):e2141779. doi:10.1001/jamanetworkopen.2021.41779
42. Hansen CL, Chaves SS, Demont C, Viboud C. Mortality associated with influenza and respiratory syncytial virus in the US. *JAMA Network Open*. 2022;5(2):e220527. doi:10.1001/jamanetworkopen.2022.0527
43. Hansen CL, Viboud C, Chaves SS. The use of death certificate data to characterize mortality associated with respiratory syncytial virus, unspecified bronchiolitis, and influenza in the United States, 1999–2018. *J Infect Dis*. 2022;226(suppl ment 2):S255-S266. doi:10.1093/infdis/jiac187
44. Reichert H, Suh M, Jiang X, et al. Mortality associated with respiratory syncytial virus, bronchiolitis, and influenza among infants in the United States: a birth cohort study from 1999 to 2018. *J Infect Dis*. 2022;226(suppl ment s):S246-S254. doi:10.1093/infdis/jiac127
45. Simões EAF, Madhi SA, Muller WJ, et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. *Lancet Child Adolesc Health*. 2023;7(3):180-189. doi:10.1016/S2352-4642(22)00321-2
46. Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *N Engl J Med*. 2023;388(16):1451-1464. doi:10.1056/NEJMoa2216480
47. Jones J Evidence to recommendations framework: Nirsevimab. Presented at: ACIP General Meeting. February 2023. [cited: 24 May 2023]. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/rsv-pediatric-04-jones-508.pdf
48. Wadman M FDA advisers agree maternal RSV vaccine protects infants, but are divided on its safety. Science, AAAS; 2023. [cited: 24 May 2023]. <https://www.science.org/content/article/fda-advisers-agree-maternal-rsv-vaccine-protects-infants-divided-safety
49. Centers for Disease Control and Prevention (CDC). RSV National Trends - NREVSS. Published August 25, 2021. [cited: 7 Feb 2022]. https://www.cdc.gov/surveillance/nrevss/rsv/natl-trend.html
50. Agha R, Avner JR. Delayed seasonal RSV surge observed during the COVID-19 pandemic. *Pediatrics*. 2021;148(3):e2021052089. doi:10.1542/peds.2021-052089
51. Centers for Disease Control and Prevention (CDC). RSV Numerator Data for the US. [cited: 3 Nov 2022]. https://www.cdc.gov/surveillance/nrevss/images/trend_images/RSV14Num_Nat.htm
52. Ramachandran KM, Tsokos CP. *Mathematical Statistics with Applications*. Elsevier Academic Press; 2009.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hariharan D, Kumar VSS, Glaser EL, et al. Quality of Life Burden on United States Infants and Caregivers Due to Lower Respiratory Tract Infection and Adjusting for Selective Testing: Pilot Prospective Observational Study. *Health Sci Rep*. 2023;6:e1338. doi:10.1002/hsr2.1338