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Economic-Burden Trajectories in Commercially Insured US Infants With Respiratory Syncytial Virus Infection

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(See the Editorial Commentary by Piedra, on pages 1205–7 and See the Major Article by Simões et al., on pages 1056–70.)

Background This study evaluates the long-term respiratory syncytial virus (RSV) burden among preterm and full-term infants in the United States.

Methods Infants with birth hospitalization claims and ≥24 months of continuous enrollment were retrospectively identified in the Truven MarketScan Commercial Claims and Encounters database for the period 1 January 2004–30 September 2015. Infants with RSV infection in the first year of life (n = 38 473) were matched to controls (n = 76 825), and remaining imbalances in the number of individuals in each group were adjusted using propensity score methods. All-cause, respiratory-related, and asthma/wheezing-related 5-year average cumulative costs were measured.

Results Early premature (n = 213), premature (n = 397), late premature (*n* = 4446), and full-term (n = 33 417) RSV-infected infants were matched to 424, 791, 8875, and 66 735 controls, respectively. After 2 years since RSV diagnosis, all-cause cumulative costs for RSV-infected infants as compared to those for controls increased by $22 081 (95% confidence interval [CI], −$5800-$42 543) for early premature infants, by $14 034 (95% CI, $5095– $22 973) for premature infants, by $10 164 (95% CI, $8835–$11 493) for late premature infants, and by $5404 (95% CI, $5110–$5698) for full-term infants. The 5-year RSV burden increased to $39 490 (95% CI, $18 217–$60 764), $23 160 (95% CI, $13 002–$33 317),$13 755 (95% CI, $12 097–$15 414), and $6631 (95% CI, $6060–$7202), respectively. The RSV burden was higher when stratified by inpatient and outpatient setting and respiratory-related and asthma/wheezing-related costs.

Conclusions The RSV burden extends across cost domains and prematurity, with the greatest burden incurred by the second year of follow-up. Findings are useful in determining the cost-effectiveness of RSV therapies in development.

Keywords. Cost burden; long-term follow-up; lower respiratory tract infection.

Respiratory syncytial virus (RSV) is the primary cause of infant lower respiratory tract infections. RSV infection is the most common cause of inpatient admission among US children aged <2 years and results in a significant burden associated with outpatient and emergency department visits [1, 2]. In Medicaid recipients, the incremental healthcare cost among infants with RSV diagnosed in an inpatient setting has been estimated to be $34 132 (in 2006 dollars) in the first year following the infection; similarly, among infants with RSV infection diagnosed in an outpatient setting, the incremental economic burden has been estimated to be $3869 (in 2006 dollars) [3]. In commercially insured infants with a gestational age of ≤36 weeks [4], an average incremental burden of $9115 (in 2006 dollars) 1 year after the infection has been reported.

Infants of lower gestational and chronological ages are likely to have more-severe RSV disease and, subsequently, higher rates of healthcare resource utilization [5–9]. These risk factors also contribute to higher inpatient and outpatient healthcare costs among infants infected with RSV [3–5, 10]. More recently, McLaurin et al [5] showed in large samples of infants <1 year of age with an index RSV event but without matching controls that the average first-year RSV-specific hospitalization costs varied from $8324 (for the full-term group) to $39 354 (for the preterm group with a gestational age of <29 weeks) among Medicaid-insured infants and from $10 570 to $40 813 (all in 2014 dollars), respectively, among commercially insured infants.

These estimates might have underestimated the economic burden of RSV because, generally, the infants were not followed up for longer than the first year following the index event, and therefore the investigators did not capture further downstream costs associated with the RSV infection. Early life exposure to RSV has been associated with the development of respiratory morbidities, including asthma, wheezing, reduced pulmonary function, and allergic sensitization, for up to 13 years [8, 11, 12].

The literature is lacking any comprehensive evaluation of the longitudinal economic burden of RSV infection. Our retrospective study compared the all-cause, respiratory-related, and asthma/wheezing-related cost burden trajectories among

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infants in whom RSV infection was diagnosed to those for controls over 5 years of follow-up since the index event. We used a large nationally representative administrative claims database, focusing on US commercially insured infants with an RSV diagnosis in the first year of life and reporting estimates stratified by prematurity and chronological age.

METHODS

Data Source

The study used retrospective data on infants born from 1 January 2004 through 30 September 2015 and identified in the Truven Health MarketScan Commercial Claims and Encounters database. The MarketScan database contains claims from >300 contributing employers and 25 contributing health plans across all regions of the United States. It includes medical (eg, inpatient, physician office, and emergency department) and outpatient pharmacy utilization, as well as information on coverage enrollment and patient-level demographic characteristics among policy holders, their spouses, and their dependents. All patient-level data within the database contain synthetic identifiers to preserve patient confidentiality [13]. Owing to the encrypted retrospective nature of the data, the study was not considered by the Colorado Multiple Institutional Review Board of the University of Colorado, Denver, to involve human subjects research.

Study Sample and Design

Infants were included in the study if they had an identifiable birth hospitalization claim and at least 24 months of continuous enrollment in medical and pharmacy coverage after the hospitalization. *International Classification of Diseases, Ninth Revision* (ICD-9), diagnosis codes for RSV (079.6x, 466.11, and 480.1x) in the primary or secondary position on a medical claim were used to identify infants with an RSV diagnosis in their first year of life [4, 14]. To identify infants with unspecified bronchiolitis or pneumonia (UBP), medical claims with ICD-9 codes 466.0x, 480.9x, 485.xx, and/or 486.xx and no concurrent (within 3 days) medical claims for influenza or bacterial pneumonia (defined by ICD-9 codes 481, 482.xx, and 487.x) were used. Finally, the remaining infants did not have evidence of RSV or UBP in their claims. In cases in which a UBP diagnosis was observed up to 14 days before the first RSV diagnosis, we considered the RSV episode to have started at the time of the prior UBP diagnosis.

Because RSV seasons vary both temporally and geographically in the United States, this study defined an RSV season on the basis of each of the 10 regional determinations made by the Department of Health and Human Services [15] and the empirical distribution of RSV diagnoses in those regions as observed in the data each year. Because we noted only a slight variation in RSV seasonality across years within a region, the final empirical RSV seasonality determination was based on pooled data across all available years within a region (Supplementary Figures 11–21). To form the control group for this study, infants with UBP cases that occurred outside of the RSV season for the respective region were merged with infants without UBP or RSV diagnoses. Infants with UBP cases that occurred during the RSV season for a region were excluded from further analyses, to minimize misclassification bias. No RSV infections were omitted from the analyses, regardless of whether they occurred in or out of the RSV season.

Infants were grouped into 4 prematurity subcohorts based on gestational age [16]: (1) early premature, defined as a gestational age of 24–28 weeks; (2) premature, defined as a gestational age of 29–34 weeks; (3) late premature, defined as a gestational age of 35–36 weeks; and (4) full term, defined as a gestational age of ≥37 weeks.

Control infants were matched to RSV-infected patients on the basis of prematurity status, year of birth, and calendar quarter of birth. The date of the index event for the RSV cohort was the first RSV diagnosis date, and control patients were assigned the index date of their matched RSV-infected patient. Infants' demographic and clinical characteristics were defined over a variable period between the dates of their birth hospitalization and index RSV case. For the definitions of hemodynamically significant congenital heart disease and chronic lung disease of prematurity, we required a diagnosis code on medical claims and the prescription drug used to treat the respective condition [17].

Costs attributable to inpatient and outpatient settings, emergency department visits, and prescription drugs were measured according to 3 definitions: all-cause events, asthma/wheezing-related events, and respiratory-related events (which included asthma/wheezing events). Respiratory- and asthma/wheezing-related events were identified using ICD-9 codes for relevant conditions when they appeared on any medical claim field (Supplementary Table 1).

Statistical Methods

We used the covariate-balancing propensity score (CBPS) method to weight matched controls and RSV-infected patients and address measurable imbalances between the 2 groups [18–20]. Compared with other approaches, such as logistic regression or boosted classification and regression trees, CBPS has shown to optimize both group assignment prediction and covariate balance [21]. Covariates input in the propensity score model included clinical and healthcare utilization variables and the monthly cost trajectory before the index date.

Infant characteristics measured up to the index date were compared using weighted summary statistics. Follow-up data were segmented into monthly increments, and the weighted *surveymeans* procedure in SAS, version 9.4, was used to calculate the average cumulative cost, similar to previously conducted longitudinal follow-up studies [22, 23]. Confidence intervals

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(CIs) and *P* values for the statistical significance of differences were obtained using the variance estimates provided by the *surveymeans* procedure, which calculates a correction factor accounting for the unequal probability of selection due to the propensity score weights [24, 25].

Total average cumulative costs and differences in costs were stratified by the 4 categories of prematurity and plotted longitudinally. Subgroup analyses by prematurity were conducted in subcohorts with an RSV diagnosis in the first 0–6 months and 7–12 months of life and in their matched controls and included separate iterations of CBPS weighting. Analyses were conducted with SAS 9.4 (Cary, NC). Costs are presented in 2015 USD.

RESULTS

We identified 213 early premature, 397 premature, 4446 late premature, and 33 417 full-term RSV-infected infants, who were matched to approximately twice as many control infants (Supplementary Figure 1). The median continuous follow-up duration across premature cohort subgroups varied from 4 to 5 years since the index date. Cohorts were well matched with respect to chronological age at index diagnosis, calendar quarter, and year of birth in propensity score–weighted (Table 1) as well as unweighted analyses (Supplementary Table 2). However, in unweighted analyses, the RSV-infected subcohorts had a higher total cost before the index date and a higher proportion of infants with hemodynamically significant congenital heart disease, chronic lung disease of prematurity, or other conditions at birth. As expected, at baseline, cohorts of increased prematurity (ie, decreased gestational age) had greater proportions of infants who were part of twin or multiple births, a greater proportion who were admitted to the neonatal intensive care unit (NICU), a longer length of stay, a greater proportion who used mechanical ventilation, a greater proportion who received palivizumab prophylaxis, a higher cost, and greater proportions with chronic conditions. After propensity scoring, RSV-infected and control subgroups were well balanced within each of the 4 prematurity cohorts (Table 1). Additionally, the trajectory of total costs before the index date was also similar between RSV-infected and control groups after propensity score weighting (Supplementary Figures 2–5).

Trajectories of Average Cumulative Cost Since Birth

Since the birth hospitalization, the rate of average cost accumulation was the steepest in the first 1 year of life across propensity score–weighted prematurity cohorts; most of the average total costs were generated in that period, especially for preterm infants (Figure 1). By 6 years of age, the average total cost among RSV-infected infants was $574 385 (95% CI, $519 950–$628 820) for the early premature subcohort, $167 286 (95% CI, $154 850–$179 723) for the premature subcohort, $114 479 (95% CI, $111 581–$117 917) for the late-premature subcohort, and $28 950 (95% CI, $28 558–$29 342) for the full-term subcohort. The trajectories of average cumulative total costs since birth were higher for RSV-infected infants as compared to controls and were significantly different in later years, as evidenced by nonoverlapping CIs, except for the early premature group.

Trajectories of Average Cumulative Cost Since date of RSV Diagnosis

Examination of average cumulative costs among RSV-infected infants and matched controls since the index date revealed that subgroups with increased prematurity consistently had higher costs, with RSV-infected subcohorts' trajectories being higher than that of their control counterparts (Figure 2). Similarly, higher asthma/wheezing-related and respiratory-related average cumulative costs since index were observed among RSV-infected infants as compared to matched controls (Supplementary Figures 6 and 7).

Difference in Average Cumulative Costs Between RSV and Controls Since Date of RSV Diagnosis: the RSV-Attributable Cost Burden

By 60 months of follow-up since index, the all-cause total cost burden was significantly higher for RSV-infected infants than for controls, with an attributable difference of $39 490 (95% CI, $18 217–$60 764) for the early premature subgroup, $23 160 (95% CI, $13 002–$33 317) for the premature subgroup, $13 755 (95% CI, $12 097–$15 414) for the late-premature subgroup, and $6631 (95% CI, $6060–$7202) for the full-term subgroup (Table 2). Accounting for more than half of the attributable all-cause economic burden of RSV by 60 months of follow-up, the respiratory-related burden was also significantly higher, with an attributable difference of $26 642 (95% CI, $12 016–$41 269) for the early premature subgroup, $12 854 (95% CI, $9050–$16 659) for the premature subgroup, $8811 (95% CI, $7992–$9630) for the late premature subgroup, and $4284 (95% CI, $4015–$4553) for the full-term subgroup. The asthma/wheezing-related burden of RSV was also significantly higher as compared to that for controls but generally represented <20% of the total all-cause economic burden. The RSV-attributable economic burden was higher at 12 and 24 months of follow-up, as well, with the exception for the all-cause cost comparison among early premature infants.

Generally, the interpretation of results in the 4 main prematurity subgroups held true for infants with an index diagnosis during ages 0–6 months or 7–12 months, as well (Supplementary Tables 3 and 4). The trajectories of the difference in average cumulative costs by prematurity status and diagnosis in the first and second 6 months of life were plotted and are available in Supplementary Figures 8–10.

RSV-Attributable Cost Burden, by Treatment Setting

Of note, the RSV-attributable all-cause economic burden among early premature and premature infants was largely generated in an inpatient setting, especially in the first year of follow-up. In contrast, the RSV-attributable all-cause economic burden in the outpatient setting was much more prominent among late-premature

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Table 1. Descriptive Characteristics of Respiratory Syncytial Virus (RSV)–Infected Infants and Matched Controls After Propensity Score Weighting, by Prematurity Status

	Early Premature			Premature			Late Premature			Full Term		
Variable	RSV (n = 213)	Control (n = 424)[a]	*P*	RSV (n = 397)	Control (n = 791)[a]	*P*	RSV (n = 4446)	Control (n = 8875)[a]	*P*	RSV (n = 33 417)	Control (n = 66 735)[a]	*P*
Continuous follow-up since diagnosis, y												
Mean ± SD	4.91 ± 2.06	5.51 ± 2.50	.001	4.73 ± 2.00	4.96 ± 2.49	.082	5.01 ± 2.13	5.43 ± 2.53	<.001	4.91 ± 2.05	5.39 ± 2.18	<.001
Median (IQR)	4.31 (3.2–6.1)	5.00 (3.7–7.0)		4.13 (3.2–5.7)	4.40 (3.4–5.9)		4.42 (3.3–6.1)	4.97 (3.6–6.8)		4.30 (3.29–5.99)	4.88 (3.59–6.70)	
Range	2.00–11.67	2.08–11.50		2.08–11.33	2.08–11.67		2.00–11.67	2.00–11.67		2.00–11.67	2.00–11.67	
Time from birth to diagnosis of index RSV event, d												
Mean ± SD	203.42 ± 92.57	204.17 ± 103.92	.926	187.95 ± 97.41	189.32 ± 115.78	.83	177.06 ± 96.00	179.77 ± 110.73	.145	171.92 ± 94.26	172.41 ± 94.27	.453
Median (IQR)	210.5 (131.5–275.5)	209.9 (136.9–271.5)		184.17 (102.2–269.5)	184.25 (105.2–270.1)		168.4 (96.9–250.9)	173.2 (99.4–252.9)		163.69 (95.4–241.6)	164.3 (95.9–242.2)	
Range	0.00–373.0	0.00–373.0		0.00–373.0	0.00–373.0		0.00–374.0	0.0–374.0		0.0–374.0	0.00–374.00	
Chronological age at time of index RSV event												
1 mo	3.76	4.48	>.999	5.80	5.63	>.999	8.23	7.62	>.999	9.09	8.98	>.999
2 mo	4.23	3.44		10.83	10.75		9.40	9.02		8.88	8.85	
3 mo	8.45	7.40		8.56	8.39		9.63	9.59		9.87	9.85	
4 mo	9.39	8.52		7.81	8.28		9.47	9.47		10.70	10.65	
5 mo	8.45	8.23		8.31	7.68		11.36	11.12		11.58	11.56	
6 mo	8.45	8.41		12.59	13.33		9.40	9.65		10.47	10.52	
7 mo	16.43	19.54		8.82	8.54		10.08	10.03		9.40	9.41	
8 mo	10.33	9.61		8.31	7.97		8.43	8.81		7.98	8.03	
9 mo	8.92	9.64		9.07	9.01		7.24	7.37		6.78	6.76	
10 mo	7.98	7.55		7.81	7.04		6.32	6.45		6.17	6.23	
11 mo	7.04	7.42		5.79	6.99		5.76	6.09		5.19	5.20	
12 mo	6.57	5.77		6.30	6.38		4.68	4.78		3.88	3.94	
Calendar year of birth												
2004	5.63	5.89	.997	3.02	3.05	>.999	5.85	5.48	.998	4.60	4.46	.954
2005	7.98	8.21		6.05	6.45		6.61	6.65		5.82	5.70	
2006	7.51	6.92		6.05	5.14		8.10	8.49		8.28	8.41	
2007	8.45	9.41		7.81	7.70		11.25	11.41		11.07	11.14	
2008	17.37	20.32		9.07	9.64		14.39	14.29		12.71	12.80	
2009	15.96	14.40		17.88	17.84		15.00	14.83		15.78	15.76	
2010	11.27	9.64		13.10	13.77		14.04	14.14		14.23	14.38	
2011	15.96	16.08		19.14	19.77		13.43	13.33		14.30	14.27	
2012	9.39	8.80		15.87	14.89		9.81	9.86		11.66	11.61	
2013	0.47	0.32		2.02	1.76		1.53	1.51		1.54	1.47	
Calendar quarter of birth												
Jan–Mar	23.00	21.46	.961	24.43	25.20	.985	26.07	26.05	>.999	24.36	24.36	.999
April–Jun	29.58	31.32		26.95	26.13		25.93	26.04		25.04	25.08	

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Table 1. Continued

	Early Premature			Premature			Late Premature			Full Term		
Variable	RSV (n = 213)	Control (n = 424)[a]	*P*	RSV (n = 397)	Control (n = 791)[a]	*P*	RSV (n = 4446)	Control (n = 8875)[a]	*P*	RSV (n = 33 417)	Control (n = 66 735)[a]	*P*
July–Sept	27.70	27.00		25.94	25.55		27.94	27.93		29.20	29.20	
Oct–Dec	19.72	20.22		22.67	23.12		20.06	19.98		21.40	21.36	
Sex												
Male	49.30	47.01	.612	58.44	58.04	.901	59.74	59.62	.901	57.24	57.17	.828
Female	50.70	52.99		41.56	41.96		40.26	40.38		42.76	42.83	
Region												
Northeast	15.49	17.04	.856	24.43	24.19	.999	13.70	13.84	>.999	15.43	15.48	>.999
North Central	25.35	24.14		21.91	22.45		20.72	20.71		23.47	23.41	
South	41.78	39.87		37.78	38.03		51.98	51.93		49.83	49.85	
West	15.02	17.44		13.10	12.55		12.06	11.99		9.85	9.85	
Unknown	2.35	1.50		2.77	2.78		1.55	1.53		1.41	1.42	
Birth status												
Multiple	3.76	5.62	.659	3.78	3.40	.921	1.62	1.84	.463	0.01	0.01	.999
Single	74.18	73.28		69.02	70.09		75.46	76.10		98.38	98.37	
Twin	22.07	21.10		27.20	26.52		22.92	22.06		1.61	1.62	
Mechanical ventilation before index RSV event	62.44	60.29	.621	30.48	29.80	.828	21.41	21.03	.659	1.40	1.26	.134
NICU admission in first mo of life	29.58	28.91	.874	13.85	13.42	.847	13.83	13.43	.558	1.36	1.05	<.001
Length of NICU stay during first mo of life, days												
Mean ± SD	76.81 ± 49.12	71.55 ± 44.75	.496	30.45 ± 33.66	26.73 ± 24.24	.464	21.06 ± 22.67	20.69 ± 29.64	.776	7.96 ± 7.64)	12.35 ± 43.14	.376
Median (IQR)	71.75 (30.88–111.25)	78.24 (30.83–100.93)		19.75 (13.75–30.63)	19.58 (13.29–36.56)		13.10 (7.48–23.69)	13.66 (7.29–23.89)		5.51 (3.50–8.69)	4.91 (3.21–7.80)	
Range	4.00–207.00	2.00–223.00		4.00–204.00	4.00–113.00		1.00–181.00	1.00–205.00		1.00–72.00	1.00–332.00	
Prophylaxis with palivizumab	49.77	49.32	.922	37.53	37.47	.986	16.89	16.82	.926	0.30	0.27	.615
Total cost before the index RSV event, 2015 $												
Mean ± SD	464 802 ± 525 142	415 604 ± 579 050	.282	105 217 ± 141 811	96 748 ± 133 137	.322	70 780 ± 133 151	67 631 ± 358 098	.463	7542 ± 29 159	7439 ± 49 836	.866
Median (IQR)	347 829 (181 761–590 527)	296 775 (142 471–532 386)		64 467 (34 353–117 131)	61 029 (31 274–123 806)		27 564 (8138–73 497)	24 086 (6839–70 245)		4047 (2838–6022)	3710 (2635–5373)	
Range	548–4 750 939	55–3 331 110		1798–1 776 912	1983–1 077 244		0–2 301 175	0–2 333 025		0–2 192 423	0–3 268 851	
Any condition before index	73.71	69.82	.33	31.74	31.92	.956	19.41	19.47	.948	2.25	2.21	.715
HS congenital heart disease	0.00	0.00		1.26	0.91	.719	0.74	0.90	.435	0.24	0.22	.783
CLD of prematurity	31.92	30.92	.821	14.86	14.14	.795	6.03	6.58	.349	0.47	0.46	.812
HIV infection	0.00	0.00		0.00	0.00		0.00	0.00		0.00	0.01	.591
Trisomy 21	0.00	0.00	>.999	1.01	0.71	.61	1.06	1.01	.832	0.30	0.29	.73
Intraventricular hemorrhage	24.41	23.84	.887	6.55	6.60	.976	3.96	3.81	.715	0.07	0.06	.608

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Table 1. Continued

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Necrotizing enterocolitis	10.80	8.29	.365	2.27	2.47	.84	1.24	1.40	.548	0.03	0.03	.56
Hydrocephalus	4.23	3.27	.587	0.76	0.88	.826	0.67	0.95	.173	0.14	0.12	.643
Periventricular leukomalacia	2.82	1.93	.489	1.51	0.65	.218	0.56	0.45	.447	0.00	0.00	.715
Retinopathy of prematurity	58.69	54.74	.376	14.86	15.61	.757	9.24	9.32	.903	0.03	0.03	.983
Sensorineural hearing loss	4.23	2.03	.143	1.51	1.89	.7	1.51	1.45	.841	0.86	0.82	.513
Cerebral palsy	2.35	0.57	.157	0.25	0.68	.372	0.22	0.14	.317	0.06	0.07	.719
Muscular dystrophy	0.00	0.00		0.00	0.11	.5	0.09	0.04	.177	0.03	0.03	.925
Anterior horn cell disease	0.00	0.00		0.00	0.00		0.02	0.01	.758	0.01	0.00	.305
Immunodeficiency	0.47	0.15	.389	0.25	0.24	.962	0.31	0.27	.721	0.11	0.11	.942
Sickle-cell anemia	0.47	0.00	.158	0.50	0.00	.046	0.31	0.22	.385	0.11	0.12	.819
Cystic fibrosis	0.00	0.00		0.00	0.15	.433	0.00	0.01	.522	0.01	0.01	.933
Failure to thrive	0.00	0.00		0.00	0.00		0.00	0.01	.591	0.01	0.00	.334
Other neuromuscular, immunological, genetic condition	0.00	0.06	.722	0.00	0.00		0.11	0.15	.546	0.07	0.08	.376

Data are (%) of infants, unless otherwise indicated.

Abbreviations: CLD, chronic lung disease; HIV, human immunodeficiency virus; HS, hemodynamically significant; IQR, interquartile range; NICU, neonatal intensive care unit.

[a]After propensity score weighting, the effective sample size for the control group was 294 for the early premature group, 592 for the premature group, 6727 for the late-premature group, and 57 128 for the full-term group.

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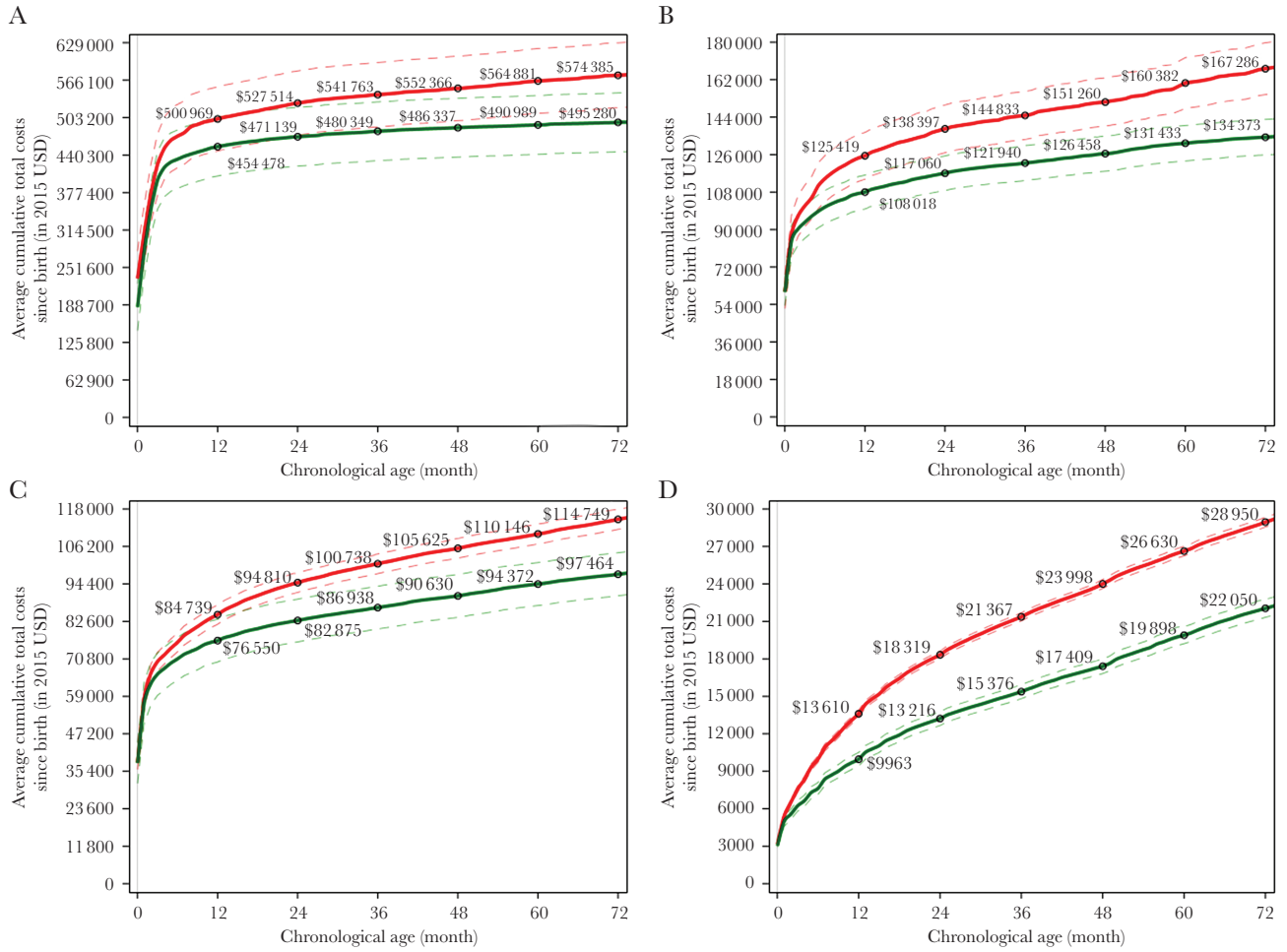

Figure 1. Average cumulative all-cause cost since birth after propensity score weighting among respiratory syncytial virus (RSV)–infected infants (top curve) and matched controls (bottom curve), by prematurity status. *A*, Early premature subcohorts. *B*, Premature subcohorts. *C*, Late premature subcohorts. *D*, Full-term cohorts. Dashed lines represent 95% confidence intervals. USD, US dollars.

infants ($5504 by month 60) and full-term infants ($2415 by month 60) and, in later years, was comparable to the burden in the inpatient setting ($5034 for late-premature infants and $2739 for full-term infants by month 60). The RSV-attributable outpatient cost burden also increased substantially for early premature and premature infants in later years of follow-up and, by month 60, represented about half of the inpatient burden in those groups.

Emergency department visit costs contributed 2%–7% of the overall cost differentials, whereas prescription drug costs contributed 15%–19%. Similar trends were also observed for the respiratory-related definition of economic burden, although inpatient setting accounted for a much higher proportion of the respiratory burden (Table 2).

DISCUSSION

Critical knowledge gaps still remain in our understanding of RSV epidemiology and the long-term impact of the infection in the United States [26] and globally [27]. Aligned with research priorities to comprehensively examine outcomes that extend beyond just the immediate effect of the acute disease and to follow-up infants until 6 years of age [28], we studied the long-term cost burden of RSV in commercially insured infants in the United States. Results from this economic analysis are in line with those from another recent study by the same research team, which found significant, long-term burden of RSV-associated healthcare utilization for all gestational ages [29]. Given that most of the costs are incurred in the first 2 years of life, we propose that most of the impact of RSV prevention efforts will be captured by prospectively studying children for the first 2 years after the intervention.

Burden estimates from both studies clearly demonstrate that the spectrum of end points collected in randomized clinical trials of RSV treatment and prevention efforts should be expanded [30]. Overall, by 60 months of follow-up, respiratory-related costs accounted for 67% of the attributable all-cause burden in the early premature cohort, 55% in the premature subcohort, and approximately 64% in the late-premature and full-term subcohorts (Table 2). The difference between the all-cause and nonrespiratory-associated healthcare utilization

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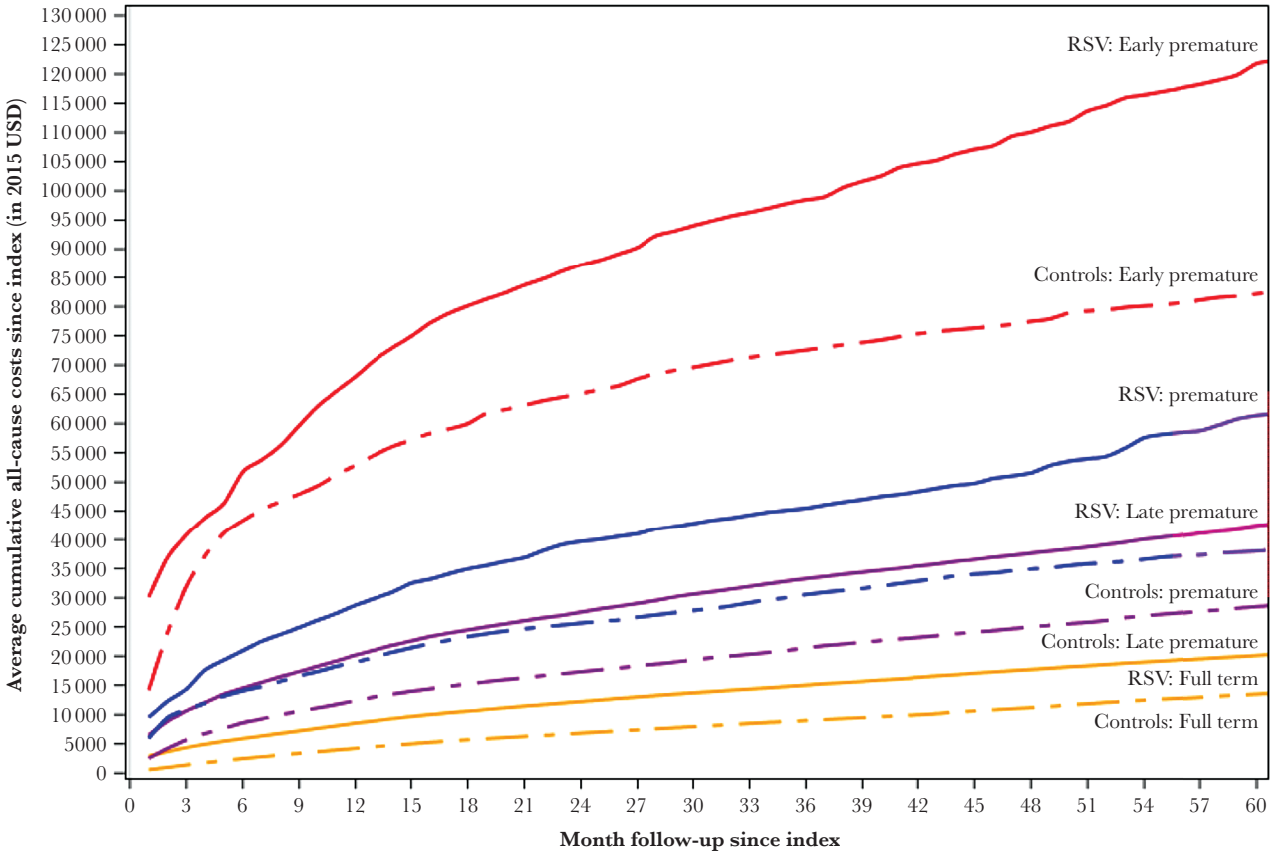

Figure 2. Average cumulative all-cause costs since the respiratory syncytial virus (RSV) infection index date after propensity score weighting, by prematurity status.

burdens was mostly due to routine child health examinations and vaccinations and conditions relating to the upper respiratory tract, which we conservatively excluded from the respiratory-related definition.

The asthma/wheezing burden in our study accounted for only 9%–19% of the total burden. Most studies examining the long-term impact of RSV examine its impact on recurrent wheezing or asthma [12]. Two current studies of palivizumab prophylaxis have followed children up to 6 years of age [31, 32] but showed no impact on asthma.

Our findings extend the evidence on the impact of RSV disease among infants of lower gestational and chronological ages [5]. We showed that, during the 5 years after the RSV index date, the respiratory burden attributable to RSV ranged from 2.1 times greater in the late-premature subcohort (cost, $8811) to 6.2 times greater in the early premature subcohort (cost, $26 642), compared with that in the full-term subcohort (cost, $4284). Relative comparisons across prematurity cohorts were similar with respect to the overall all-cause cost burden definition. Although the absolute cost impact of RSV was greatest among infants infected in the first 6 months of life (Supplementary Table 3), consistent with conclusions by other studies [9], results of relative comparisons of the RSV-attributable burden across higher-risk prematurity cohorts were similar to those for the main gestational cohorts, with a 1.7 times greater burden in the late-premature subcohort (cost, $15 085) and a 6.0 times greater burden in the early premature subcohort (cost, $57 274), compared with that in the full-term subcohort (cost, $8973).

Infants infected with RSV during the second 6 months of life incurred >50% of their attributable cost burden between 24 and 60 months of follow-up (Supplementary Table 4), compared with infants infected during the first 6 months of life, in whom most of the attributable cost burden occurred during the first 24 months (Supplementary Table 3). This stems from the fact that RSV-infected and control groups with disease diagnosed during 0–6 months of chronological age also coincidentally and naturally accumulate very high costs in early life, dwarfing any further cost generation in later months of follow-up. For comparison, the accumulation of costs after diagnosis for those with disease diagnosed during 7–12 months of life is much more gradual, coinciding with a lower need for medical attention and healthcare utilization in later life, and hence cost differences between RSV-infected infants and controls are much more gradual (Supplementary Figure 22).

Interestingly, RSV infection in the second 6 months of life resulted in higher point estimates of incremental asthma/wheezing-related costs in all 4 prematurity subgroups at all

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Table 2. Difference in Average Cumulative Costs Between Infants With Respiratory Syncytial Virus (RSV) Infection and Matched Controls, by Time Since RSV Event

Prematurity Status, Follow-up, Setting	Cost Difference, $ (95% CI)		
	All-Cause Costs	Respiratory-Related Costs	Asthma/Wheezing-Related Costs
Early premature			
12 mo			
Inpatient setting	12 192 (–7636–32 019)	18 913 (4458–33 368)	858 (–117–1834)
Outpatient setting	459 (–1860–2779)	1066 (425–1706)	394 (229–559)
ED	301 (164–438)	152 (71–232)	52 (14–90)
Pharmacy	2207 (1295–3119)	596 (472–720)	415 (326–503)
Total	15 159 (–4924–35 242)	20 726 (6255–35 197)	1719 (708–2730)
24 mo			
Inpatient setting	14 286 (–5799–34 372)	20 042 (5524–34 560)	1447 (278–2616)
Outpatient setting	4446 (1583–7309)	1291 (523–2058)	475 (219–731)
ED	528 (334–722)	224 (122–325)	94 (39–150)
Pharmacy	2822 (1816–3827)	980 (818–1143)	661 (547–774)
Total	22 081 (–5800–42 543)	22 537 (7994–37 080)	2677 (1458–3897)
60 mo			
Inpatient setting	20 913 (369–41 456)	22 027 (7438–36 617)	2156 (778–3535)
Outpatient setting	11 696 (7572–15 819)	2045 (1149–2942)	850 (549–1152)
ED	839 (526–1151)	361 (207–516)	175 (67–283)
Pharmacy	6043 (4721–7365)	2240 (1885–2594)	1216 (1058–1374)
Total	39 490 (18 217–60 764)	26 642 (12 016–41 269)	4378 (2933–5824)
Premature			
12 mo			
Inpatient setting	8361 (1–16 722)	7581 (4011–11 151)	414 (–30–868)
Outpatient setting	184 (–1195–1562)	777 (642–912)	77 (33–121)
ED	203 (99–308)	144 (84–204)	11 (–6–27)
Pharmacy	1006 (572–1441)	272 (217–327)	189 (148–229)
Total	9755 (1205–18 304)	8774 (5189–12 359)	691 (224–1157)
24 mo			
Inpatient setting	12 306 (3710–20 902)	9445 (5715–13 174)	503 (42–965)
Outpatient setting	32 (–1959–2022)	1113 (909–1317)	206 (71–340)
ED	313 (182–443)	180 (113–247)	27 (1–54)
Pharmacy	1383 (919–1847)	425 (349–501)	310 (256–364)
Total	14 034 (5095–22 973)	11 163 (7412–14 914)	1046 (552–1541)
60 mo			
Inpatient setting	12 834 (3923–21 746)	9762 (5987–13 536)	737 (184–1291)
Outpatient setting	6358 (2328–10 387)	1553 (1298–1808)	426 (233–620)
ED	551 (341–761)	287 (187–388)	72 (11–132)
Pharmacy	3418 (2850–3986)	1259 (1080–1437)	945 (799–1090)
Total	23 160 (13 002–33 317)	12 854 (9050–16 659)	2166 (1545–2786)
Late premature			
12 mo			
Inpatient setting	3709 (2537–4882)	4705 (4069–5340)	278 (203–353)
Outpatient setting	2686 (2389–2982)	1056 (978–1134)	196 (173–220)
ED	290 (260–320)	182 (165–199)	37 (29–45)
Pharmacy	1033 (869–1197)	367 (348–385)	233 (219–247)
Total	7718 (6469–8967)	6309 (5663–6956)	744 (661–828)
24 mo			
Inpatient setting	4494 (3270–5719)	5052 (4387–5717)	411 (317–506)
Outpatient setting	3948 (3575–4322)	1321 (1233–1408)	343 (309–378)
ED	422 (381–467)	245 (222–264)	75 (62–89)
Pharmacy	1299 (1120–1477)	679 (653–705)	444 (424–463)
Total	10 164 (8835–11 493)	7297 (6619–7974)	1274 (1166–1381)
60 mo			
Inpatient setting	5034 (3555–6513)	5454 (4648–6260)	662 (526–799)
Outpatient setting	5504 (4937–6071)	1687 (1576–1797)	598 (536–660)

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Table 2. Continued

Prematurity Status, Follow-up, Setting	Cost Difference, $ (95% CI)		
	All-Cause Costs	Respiratory-Related Costs	Asthma/Wheezing-Related Costs
ED	666 (603–730)	341 (311–371)	135 (115–155)
Pharmacy	2554 (2339–2769)	1338 (1292–1384)	913 (879–947)
Total	13 755 (12 097–15 414)	8811 (7992–9630)	2298 (2138–2457)
Full term			
12 mo			
Inpatient setting	2399 (2162–2636)	2119 (1954–2284)	155 (126–184)
Outpatient setting	1341 (1272–1411)	583 (560–606)	126 (121–132)
ED	227 (216–238)	156 (150–162)	23 (21–25)
Pharmacy	327 (279–375)	241 (236–246)	144 (140–147)
Total	4295 (4033–4557)	3099 (2930–3268)	448 (418–479)
24 mo			
Inpatient setting	2665 (2408–2922)	2313 (2135–2490)	222 (190–254)
Outpatient setting	1868 (1767–1969)	700 (670–730)	199 (191–207)
ED	302 (288–315)	191 (184–198)	40 (37–43)
Pharmacy	570 (520–620)	428 (421–434)	266 (261–271)
Total	5404 (5110–5698)	3631 (3448–3815)	727 (693–761)
60 mo			
Inpatient setting	2739 (2248–3230)	2417 (2165–2669)	322 (279–366)
Outpatient setting	2415 (2206–2624)	825 (762–889)	344 (331–357)
ED	443 (422–464)	247 (237–256)	73 (67–78)
Pharmacy	1036 (975–1096)	798 (786–810)	512 (503–521)
Total	6631 (6060–7202)	4284 (4015–4553)	1245 (1198–1293)

Abbreviations: CI, confidence interval; ED, emergency department.

time points (12, 24, and 60 months; Supplementary Table 4), compared with the incremental costs for infants developing an RSV infection in the first 6 months of life (Supplementary Table 3). Given the known association between the development of RSV infection in the first 6 months of life and subsequent recurrent wheezing, this finding might suggest that preventing RSV infection in the first year of life could have important cost savings not only for the most-premature infants but also for full-term infants.

Such cost comparisons are very important in the context of the value of any current or future RSV-associated treatment and preventive regimens. Presently, no vaccine is available to prevent RSV infection, and immunoprophylaxis with the neutralizing monoclonal antibody palivizumab is limited to infants born very prematurely and/or with specific congenital conditions. However, the cost of weight-dependent dosing over multiple months makes use of palivizumab impractical in low- and middle-income countries [33].

From a US payer perspective, the estimated average 2016–2017 cost of palivizumab treatment for otherwise healthy preterm infants born at a gestational age of 29–35 weeks has been estimated to range from $3221 to $12 568, depending on dosing regimen, gestational age in weeks, and birth month [34]. Other studies estimate immunoprophylaxis with palivizumab costs as much as $6000–$20 000 per child for 4–5 doses during 1 RSV season [35, 36]. While variation in the cost of palivizumab seems substantial, findings from our study provide evidence that immunoprophylaxis for preterm infants at risk of RSV infection in the first 6 months of life may be cost saving for the healthcare system because lower-weight infants would require smaller doses, which would lower the cost of prophylaxis [36]. Restricting RSV immunoprophylaxis to preterm infants with gestational age of ≤28 weeks or those 29–34 weeks with qualifying conditions of hemodynamically significant congential heart disease or chronic lung disease of prematurity, as recommended by the American Academy of Pediatrics in 2014, was a correlate of a multifold observed increase in RSV hospitalizations during the year after implementing the restriction and might have especially affected infants with a gestational age of 29–34 weeks and a chronological age of <3 months during the RSV season [37].

The current cost of immunoprophylaxis, however, makes it prohibitive to passively immunize all infants of any gestational or chronological age. An economic appraisal from Europe determined that targeted RSV prophylaxis is not cost-effective at reducing the RSV burden in moderately preterm infants unless lower-priced biosimilar palivizumab or vaccine is available [38]. Another study [39] concluded that the maximum price per fully protected person that should be paid for infant, newborn, and maternal immunization strategies without seasonal restrictions should be £192 ($249), £81 ($105), and £54 ($70), respectively. Future US analyses of the cost-effectiveness of vaccines can use

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data reported in our study to examine the maximum price per fully protected person for the United States.

The general limitations of using administrative claims data for research purposes apply to our study, and residual misclassification bias is possible. Additionally, some of the included infants had received palivizumab prophylaxis during their first year of life, which might have influenced outcomes observed for preterm infants even after incorporating matching procedures. Last but not least, our study may not be entirely generalizable for the United States because it did not include Medicaid recipients. Prior evidence suggests that the average costs for Medicaid-insured infants may be somewhat lower than those for commercially insured infants, possibly explained by lower reimbursement rates [5].

With vaccine and prophylactic agents for RSV likely becoming available in the next 5 years, this study bridges the critical knowledge gap regarding the long-term impact of RSV in commercially insured preterm and full-term infants in the United States. We found that the long-term burden of RSV may not be restricted to only asthma/wheezing and respiratory disease but also extends across all cost domains, including inpatient setting, outpatient setting, emergency department, and prescription drug utilization. Clinical guideline societies, payers, and vaccine trialists should use findings from this study to best inform decisions regarding the cost-effectiveness of prevention and management of RSV infection.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. E. A. F. S. reports grants and personal fees from Abbvie, Medimmune, Regeneron Pharmaceuticals, Pfizer, and Merck to the University of Colorado and grants from Novavax to the University of Colorado, all outside the submitted work. V. V. C. is an employee of Pharmerit International, which received research funding for the current study. M. B. is an employee and shareholder of Pharmerit and reports grants from Regeneron Pharmaceuticals, all during the conduct of the study; and reports grants from Regeneron and AbbVie, both outside the submitted work. Y. K. is an employee of Pharmerit International, which received research funding for the current study. A. K. is an employee of and stockholder in Regeneron Pharmaceuticals.

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.

References

1. Walsh EE. Respiratory syncytial virus infection: an illness for all ages. Clin Chest Med **2017**; 38:29–36.
2. Hall CB, Simões EA, Anderson LJ. Clinical and epidemiologic features of respiratory syncytial virus. Curr Top Microbiol Immunol **2013**; 372:39–57.
3. Shi N, Palmer L, Chu BC, et al. Association of RSV lower respiratory tract infection and subsequent healthcare use and costs: a Medicaid claims analysis in early-preterm, late-preterm, and full-term infants. J Med Econ **2011**; 14:335–40.
4. Stewart DL, Romero JR, Buysman EK, Fernandes AW, Mahadevia PJ. Total healthcare costs in the US for preterm infants with respiratory syncytial virus lower respiratory infection in the first year of life requiring medical attention. Curr Med Res Opin **2009**; 25:2795–804.
5. 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**; 36:990–6.
6. Stein RT, Bont LJ, Zar H, et al. Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. Pediatr Pulmonol **2017**; 52:556–69.
7. Simões EA, Anderson EJ, Wu X, Ambrose CS. Effects of chronologic age and young child exposure on respiratory syncytial virus disease among US preterm infants born at 32 to 35 weeks gestation. PLoS One **2016**; 11:e0166226.
8. Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. Pediatr Allergy Immunol **2005**; 16:386–92.
9. Parikh RC, McLaurin KK, Margulis AV, et al. Chronologic age at hospitalization for respiratory syncytial virus among preterm and term infants in the United States. Infect Dis Ther **2017**; 6:477–86.
10. Palmer L, Hall CB, Katkin JP, et al. Healthcare costs within a year of respiratory syncytial virus among Medicaid infants. Pediatr Pulmonol **2010**; 45:772–81.
11. Sigurs N, Aljassim F, Kjellman B, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax **2010**; 65:1045–52.
12. Fauroux B, Simões EAF, Checchia PA, et al. The burden and long-term respiratory morbidity associated with respiratory syncytial virus infection in early childhood. Infect Dis Ther **2017**; 6:173–97.
13. Truven Health Analytics. The Truven Health MarketScan Databases for Health Services Researchers. Overview of MarketScan claims data. **2019**. https://truvenhealth.com/portals/0/assets/2017_MarketScan_Databases_Health_Services_Researchers.pdf. Accessed February 2014.
14. Winterstein AG, Knox CA, Kubilis P, Hampp C. Appropriateness of age thresholds for respiratory syncytial

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virus immunoprophylaxis in moderate-preterm infants: a cohort study. JAMA Pediatr **2013**; 167:1118–24.
15. Centers for Disease Control Prevention. Respiratory syncytial virus activity - United States, July 2008–December 2009. MMWR Morb Mortal Wkly Rep **2010**; 59:230–3.
16. Li Q, Andrade SE, Cooper WO, et al. Validation of an algorithm to estimate gestational age in electronic health plan databases. Pharmacoepidemiol Drug Saf **2013**; 22:524–32.
17. Krilov LR, Masaquel AS, Weiner LB, Smith DM, Wade SW, Mahadevia PJ. Partial palivizumab prophylaxis and increased risk of hospitalization due to respiratory syncytial virus in a Medicaid population: a retrospective cohort analysis. BMC Pediatr **2014**; 14:261.
18. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology **2000**; 11:561–70.
19. Austin PC. A tutorial and case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. Multivariate Behav Res **2011**; 46:119–51.
20. Imai K, Ratkovic M. Covariate balancing propensity score. J R Stat Soc Series B Stat Methodol **2014**; 76:243–63.
21. Wyss R, Ellis AR, Brookhart MA, et al. The role of prediction modeling in propensity score estimation: an evaluation of logistic regression, bCART, and the covariate-balancing propensity score. Am J Epidemiol **2014**; 180:645–55.
22. Griffiths RI, Gleeson ML, Mikhael J, Dreyling MH, Danese MD. Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma. Cancer **2012**; 118:6079–88.
23. Griffiths RI, Gleeson ML, Danese MD, O'Hagan A. Inverse probability weighted least squares regression in the analysis of time-censored cost data: an evaluation of the approach using SEER-Medicare. Value Health **2012**; 15:656–63.
24. Dugoff EH, Schuler M, Stuart EA. Generalizing observational study results: applying propensity score methods to complex surveys. Health Serv Res **2014**; 49:284–303.
25. Bell BA, Onwuegbuzie AJ, Ferron JM, Jiao QG, Hibbard ST, Kromrey JD. Use of design effects and sample weights in complex health survey data: a review of published articles using data from 3 commonly used adolescent health surveys. Am J Public Health **2012**; 102:1399–405.
26. Kim L, Rha B, Abramson JS, et al. Identifying gaps in respiratory syncytial virus disease epidemiology in the United States prior to the introduction of vaccines. Clin Infect Dis **2017**; 65:1020–5.
27. Vekemans J, Moorthy V, Giersing B, et al. Respiratory syncytial virus vaccine research and development: World Health Organization technological roadmap and preferred product characteristics. Vaccine **2018**; pii: S0264-410X(17)31364-6.
28. Karron RA, Zar HJ. Determining the outcomes of interventions to prevent respiratory syncytial virus disease in children: what to measure? Lancet Respir Med **2018**; 6:65–74.
29. Simões EA, Chirikov VV, Kwon Y, Botteman MF, Kuznik A. Long-term assessment of healthcare utilization five years after respiratory syncytial virus infection in US infants. Presented at: 11th International RSV Symposium, Asheville, North Carolina, 31 October –4 November 2018.
30. Simões EA, Carbonell-Estrany X, Guilbert T, et al. Clinical endpoints for respiratory syncytial virus prophylaxis trials in infants and children in high-income and middle-income countries. Pediatr Infect Dis J **2015**; 34:1086–92.
31. Mochizuki H, Kusuda S, Okada K, Yoshihara S, Furuya H, Simões EAF; Scientific Committee for Elucidation of Infantile Asthma. Palivizumab prophylaxis in preterm infants and subsequent recurrent wheezing. Six-year follow-up study. Am J Respir Crit Care Med **2017**; 196:29–38.
32. Scheltema NM, Nibbelke EE, Pouw J, et al. Respiratory syncytial virus prevention and asthma in healthy preterm infants: a randomised controlled trial. Lancet Respir Med **2018**; 6:257–64.
33. Higgins D, Trujillo C, Keech C. Advances in RSV vaccine research and development - a global agenda. Vaccine **2016**; 34:2870–5.
34. Shahabi A, Peneva D, Incerti D, McLaurin K, Stevens W. Assessing variation in the cost of palivizumab for respiratory syncytial virus prevention in preterm infants. Pharmacoecon Open **2017**; 1–9.
35. Haynes LM. Progress and challenges in RSV prophylaxis and vaccine development. J Infect Dis **2013**; 208(Suppl 3):S177–83.
36. Olchanski N, Hansen R, Pope E, et al. Palivizumab prophylaxis for respiratory syncytial virus: examining the evidence around value. Open Forum Infect Dis **2018**; 5:ofy031.
37. Kong AM, Krilov LR, Fergie J, et al. The 2014–2015 national impact of the 2014 American Academy of Pediatrics guidance for respiratory syncytial virus immunoprophylaxis on preterm infants born in the United States. Am J Perinatol **2018**; 35:192–200.
38. Blanken MO, Frederix GW, Nibbelke EE, et al.; Dutch RSV Neonatal Network. Cost-effectiveness of rule-based immunoprophylaxis against respiratory syncytial virus infections in preterm infants. Eur J Pediatr **2018**; 177:133–44.
39. Cromer D, van Hoek AJ, Newall AT, Pollard AJ, Jit M. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and cost-effectiveness analysis for England. Lancet Public Health **2017**; 2:e367–74.

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