

Risk of Childhood Wheeze and Asthma after Respiratory Syncytial Virus Infection in Full-Term Infants

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Abstract (250/250 words)

Background: Most studies addressing the association between RSV and recurrent wheezing (RW) and asthma have been conducted in patients at risk for lung morbidity. Data in full-term infants is limited.

Methods: The risk of RW/asthma during the first 5 years of life in full-term infants hospitalized with RSV during the first year (Y) of life was estimated using 2010-16 data from three claims databases in USA [Truven MarketScan Commercial Claims and Encounters Database (CCAE), Truven Health MarketScan Multi-State Medicaid (MDCD), and Optum Clinformatics Extended Data Mart–Socio-Economic Status (SES)]. Full-term infants with and without RSV infection and ≥ 2 years of continuous health plan enrollment from birth were included. Incidence of RW/asthma, cumulative incidence, adjusted incidence rate ratios (aIRR), and odds ratios (aOR) were calculated.

Results: During the 16-year study, 38,494 (CCAE), 62,846 (MDCD), and 23,099 (SES) matched infant-pairs were included in each cohort. In the CCAE database, RW/asthma incidence/1000 patient-years (69.7 vs 28.7, aIRR: 2.4 [2.3-2.5]); cumulative incidence (17.6-25.2% vs. 5.0-11.4%); and aOR (Y2: 4.1 [3.9-4.4]; Y3: 3.2 [3.0-3.3]; Y4: 2.9 [2.7-3.1]; Y5: 2.6 [2.5-2.9]) were higher in the RSV vs. non-RSV cohort. Results in the SES insured population were comparable, while cumulative incidence and aIRR were higher in the Medicaid population (MDCD).

Conclusion: Although there are limitations of this study, including possible coding errors and missing covariates, we showed that full-term infants with severe RSV infection during the first year of life, spanning several respiratory seasons and a geographically diverse population, are at significant risk of RW/asthma during childhood.

Keywords: Respiratory syncytial virus, recurrent wheezing, asthma, full-term, infants

Introduction (2500/2500 words)

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infection (LRTI) in young children worldwide.¹ During the first year of life, 60 to 70% of children acquire RSV infection, and almost all children are infected by 2 years of age.^{2,3} RSV accounts for 24% of all LRTI hospitalizations in children <5 years of age, and 2.1 million outpatient visits every year.^{4,5}

In the US, each year, 1 in 6 children with asthma is evaluated in the emergency department (ED), and 1 in 20 requires hospitalization.⁶ The etiology of asthma is not fully understood; however, genetic and environmental exposures appear to be crucial. Viral infections early in life have been identified as an important risk factor for asthma development later in life.⁷

Most of the studies that highlight the association between RSV infection during early childhood and subsequent development of recurrent wheezing (RW) or asthma have focused on localized regions⁸⁻¹⁰ and either included a mixed population of children at risk of lung morbidity or have exclusively focused on premature infants, a group that is at particularly high risk both for RSV infection and pulmonary sequelae.^{4,11} The present study was conducted to investigate the association between RSV infection in the first year of life in full-term infants in the US and subsequent development of RW or asthma over 16 years using three large administrative healthcare claims databases, representing a geographically diverse population. Identification of risk factors in infancy is an important step towards disease interception and reducing the burden of RW or asthma later in life.

Methods

Data source

Data were obtained from three administrative claims databases: Truven MarketScan Commercial Claims and Encounters Database (CCAE), Truven Health MarketScan Multi-State Medicaid (MDCD), and Optum Clinformatics Extended Data Mart - Socio-Economic Status (SES). Data obtained from these databases were analyzed independently. The CCAE database primarily consists of a privately insured population, the MDCD database contains Medicaid enrollees' data from multiple states and the SES database contains data of United Healthcare

(UHC) fully insured population, UHC administrative services only, Medicaid, and legacy Medicare Choice membership and claims. These databases capture individual's enrollment information (e.g., demographics, period of enrollment, plan type), inpatient and outpatient services, medical and pharmacy claims, and financial information

All study data were accessed with protocols compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations. Because this study used only deidentified patient records, it was exempt from institutional review board approval.

Study design

For this retrospective matched-cohort study, eligible infants from the three databases were identified during the following periods: CCAE (January 1, 2000 to December 31, 2015), MDCCD (January 1, 2006 to December 31, 2015) and, SES (January 1, 2006 to September 30, 2016).

The first year of life was designated as the index period (Y1) and used to identify RSV exposure. The index period was defined as the period between date of birth (DOB $\pm$ 15 days), which was based on the insurance assignment date and the day after one year from DOB (index date). Infants were followed from the index date for the development of RW or asthma until end of enrollment, end of year 5, or end of the study period, whichever occurred first (eFigure 1).

Study population and sample selection

Infants with at least 2 years of continuous health plan enrollment with both medical and pharmacy coverage were included in the analysis. Exclusion criteria were: prematurity (gestational age <37 weeks), birth weight <2500 gm, slow fetal growth and malnutrition, congenital heart disease, congenital lung disease or respiratory system anomalies, RW or asthma during their first year of life or palivizumab immunoprophylaxis (eTable 1). Infants who met inclusion criteria were included in the RSV cohort if they had a documented RSV infection, identified by any of the following diagnosis codes: RSV (ICD-9: 079.6; ICD-10: B 97.4), acute bronchiolitis due to RSV (ICD-9: 466.11; ICD-10: J21.0), or pneumonia due to RSV (ICD-9: 480.1; ICD-10: J12.1). The non-RSV cohort included full-term healthy infants who met the

inclusion criteria but did not meet the RSV criteria defined above. In addition, the non-RSV cohort did not have any diagnosis for acute bronchitis due to RSV (ICD-9: 466.0; ICD-10: J20.5), acute bronchiolitis due to other infectious organisms (ICD-9: 466.19; ICD-10: J21.1, J21.8, J21.9), unspecified viral pneumonia (ICD-9: 480.9; ICD-10: J12.9), bronchopneumonia organism unspecified (ICD-9: 485; ICD-10: J18.0); and pneumonia, organism unspecified (ICD-9: 486; ICD-10: J18.8, J18.9), and were not hospitalized for any reason after birth during the first year of life. A sensitivity analysis was conducted excluding any matched infant-pairs with a baseline diagnosis of cystic fibrosis, Down's syndrome, immunodeficiency and other respiratory conditions of fetus and newborn.

ICD-CM-9/10, Generic Product Identifier (GPI), Current Procedural Terminology (CPT), The Healthcare Common Procedure Coding System (HCPCS), and Uniform/Universal Billing (UB) codes were used to retrieve data related to diagnoses and medication records and procedures (eTable 1).

Outcomes

Asthma was identified if there was at least one claim with the ICD-9/10 diagnosis (ICD-9: 493 [asthma], 506.3 [reactive airway disorder syndrome]; ICD-10: J45 [asthma], J68.3 [reactive airway disorder syndrome]) during the follow-up period. RW was defined as at least 3 diagnoses for wheezing (ICD-9: 786.07; ICD-10: R06.2) within the first year of follow-up, with the date of the first wheezing diagnosis considered as the index date for the RW outcome. The risk of RW or asthma during the follow-up period was assessed by estimating cumulative incidence, incidence per 1000 patient-years, time to first event, and probability of event-free survival. Cumulative incidence was defined as the proportion of infants newly diagnosed with RW or asthma.

Statistical analysis

The RSV and non-RSV cohorts were 1:1 matched based on gender, health plan type, year/month of birth, and region of residence. Differences in baseline characteristics between cohorts were tested using Chi-square or Fisher's Exact test for categorical variables and Student's t-test for continuous variables.

Cumulative incidence of RW or asthma was analyzed through each follow up year (Y) independently (Y2, Y3, Y4, Y5). Adjusted incidence rate ratios (aIRR) with 95% confidence intervals (CIs), were calculated using a general linear model, assuming Poisson distribution and logarithm link function while offsetting by at-risk time. The relation of event-free probability and at-risk years between the two cohorts was assessed using Kaplan-Meier and Cox proportional hazard models to calculate adjusted hazard ratios (aHR) with 95% CIs. Multivariable conditional logistic regression modeling was applied to calculate the adjusted odds ratios (aOR) with 95% CIs for development of RW or asthma for each follow up period. When applicable the following covariates were used for multivariable models: comorbid infections specific to perinatal period (ICD-9: 771; ICD-10: P35-P39), other respiratory conditions of fetus and newborn (ICD-9: 770; ICD-10: P23-P28), influenza vaccination, and pneumococcal vaccination. Analyses were performed using SAS Enterprise Guide, version 7 (SAS Institute., Cary, NC) and two-tail p values < 0.05 were considered statistically significant.

Results

Demographic and baseline clinical characteristics

A total of 124,439 matched infant-pairs were included; 38,494 in each cohort from the CCAE database, 62,846 from the MDCC database, and 23,099 from the SES database (Figure 1). Proportion of female and male infants was comparable across all three databases (females: CCAE, 45.7%; MDCC, 47.9%; SES, 46.3%). The majority of infants were born between June- and December (CCA, 65.9%; MDCC, 65.5%; SES, 68.0%) and 54% of infants enrolled in CCAE and 52.6% in the SES database were from southern states. Classification by region was not available for the MDCC database. (Table 1).

Baseline clinical characteristics were comparable between CCAE and SES databases and showed that infections specific to the perinatal period were more commonly identified in the RSV vs. non-RSV cohort (5.4% vs. 3.2% $P<.0001$) as well as other respiratory conditions of fetus and newborn (5.8% vs. 2.6%; $P<.0001$). Antibiotic (76.7% vs. 44.7%) and systemic corticosteroid therapy (continuous corticosteroid use ≥ 14 days; 24.8% vs. 5.4%) were more commonly used in the RSV vs. non-RSV cohort ($P<.0001$). Results from the MDCC database were similar except for higher prevalence of other medical conditions, and lower vaccination rate for both cohorts (Table 2).

Incidence of Recurrent Wheezing or Asthma

Mean time to first RW or asthma event was shorter in the RSV vs non-RSV cohort in all three databases: CCAE database (17.9 vs. 25.4 months; aHR [95% CI]: 2.4 [2.3–2.5]). Similarly, the aHR was 2.6 (95% CI: 2.5–2.6) times higher in the MDCC database, and 2.2 (95% CI: 2.1–2.4) times higher in the SES database. Density plots showed that asthma/RW occurred earlier in the RSV than in the non-RSV cohort, and although the event-free probabilities continued to deviate at a slower pace over time, differences remained significant between groups until Y5 (Figure 2).

Incidence rate of RW/asthma per 1000 patient-years was higher in the RSV cohort in all three databases with a higher increase in the MDCC population. In the CCAE database, incidence rate in the RSV vs. non-RSV cohort was 69.7 vs. 28.7 (aIRR [95% CI]: 2.4 [2.3–2.5]). Comparable results were observed in the SES population (RSV vs. non-RSV: 69.0 vs. 30.3; aIRR [95% CI]: 2.3 [2.2–2.4]) and even greater incidence in the MDCC population (RSV vs. non-RSV: 100.2 vs. 38.5; aIRR [95% CI]: 2.6 [2.5–2.7]) (eTable 2). In the CCAE population, cumulative incidence of RW or asthma (aOR [95% CI]) was 2–4 times higher in the RSV vs. non-RSV cohort through all follow-up periods (Y2: 17.6 vs. 5.0%, 4.1 [3.9–4.4]; Y3: 21.4 vs. 7.9%, 3.2 [3.0–3.3]; Y4: 23.8 vs. 9.7%, 2.9 [2.7–3.1]; Y5: 25.2 vs. 11.4%, 2.6 [2.5–2.9]). Results from the SES database were comparable with the CCAE population; however, in the MDCC population, cumulative incidence was higher, especially at Y4 and Y5 follow-up periods (Table 3). The gradual decrease in aOR with age suggests that the exposure to RSV had a greater impact on the risk of asthma/RW in the earlier years however, the association was still strong and significant during the follow up period.

A sensitivity analysis in which we excluded any infants with baseline comorbidities that might impact RSV/asthma risk or outcomes (n=6,214; 16%), yielded similar results as the original matched RSV/non-RSV analysis that included 124,349 matched infant- pairs (eTables-3–4).

Discussion

This large study reflecting the real world and conducted over 16 RSV seasons showed that full-term infants with RSV infection during the first year of life had a significantly high risk of developing RW or asthma during the first five years of age. Infants included in the RSV cohort had both a shorter time to the first RW or asthma episode, and a substantially higher incidence of RW or asthma during the following four years of life, compared with infants who did not have a documented RSV infection.

Studies in different populations (e.g., infants at risk for asthma, premature infants) have shown that children with RSV infection at an early age have increased risk of developing RW, asthma, or impaired lung function later in childhood, adolescence, or even adulthood.¹⁰⁻²³ Findings of the present study expand on the literature by providing important evidence of this association in an unselected cohort of full-term infants. We believe these results are generalizable since we utilized a large dataset including a geographically diverse population with both commercial or Medicaid insurance. A small percentage of infants in the initial cohort had comorbidities that could have influenced the risk for RSV infection and asthma. Nevertheless, a sensitivity analysis excluding these infants yielded similar results, indicating little impact of confounding comorbidities on the outcomes of interest.

Observational prospective and retrospective studies conducted among US infants with RSV infection have reported different rates of RW or asthma, presumably due to differences in study design, outcomes used, selected population, and duration of follow up. Among retrospective studies an Australian population-based cohort study showed that children hospitalized with RSV infection within the first 2 years of life, had a higher risk of being hospitalized for asthma at 2–3 years of age than children without a prior RSV hospitalization, irrespective of gestational age.²⁴ In addition, using claim insurance data from a single state, Escobar, et al. reported RW rates of 16.2% at 3 years and 12.5% at 5 years of age after RSV infection in children born at ≥ 32 weeks' gestation in Northern California.^{9,10} In another recent study that used data from a single administrative database and included premature and full term infants, the 5-year cumulative rate of asthma/wheezing was 10-18%.²⁵ Similarly, asthma rates of 16-23% have been documented at 6 years of age in full term infants with a history of

bronchiolitis in the first year of life during the RSV season.²⁶ Consistent with those studies, we found that the majority of infants included in the RSV cohort were born between June and December, reflecting the seasonality of RSV. Additionally, a greater proportion of infants were from southern states, perhaps due to the geographical distribution of the insurance plans represented in the databases, and the longer duration of the RSV season in Florida compared with the rest of the country.²⁷

Prospective studies have reported even higher rates. Bacharier et al¹² reported a 48% asthma rate by 7 years of age in children with severe RSV bronchiolitis at ≤ 12 months of age. In a pivotal study, Stein et al reported that RSV LRTI before 3 years of age was associated with an increased risk of wheeze by six years of age.¹¹ In four sequential reports derived from the same cohort but at different ages, Sigurs et al reported that infants with severe RSV infection during the first year of life had asthma rates significantly higher than the control group at 3, 7, 13, and 18 years of age.^{28,29,22,21} Findings of the present study highlight that an unselected population of full-term infants across the USA are also at a substantial risk of long-term lung morbidity after RSV infection with a 5-year cumulative incidence rate that varied from 24% to 35%.

Identification of RSV infection as a strong predictor of early childhood RW or asthma may contribute to improved care through targeted interventions.²³ Data derived from preclinical studies³⁰, observational studies³¹, and randomized clinical trials³² have shown that prevention of RSV infection by use of immunoprophylaxis is associated with a significant decrease of subsequent wheezing. Another potential benefit of preventing RSV infection in infancy may be a reduction of antibiotic use commonly prescribed in respiratory infections. Thus, studies for the prevention or treatment of acute RSV infection should include long-term follow-up to determine the effect of such interventions on long-term pulmonary outcomes.

This study has limitations. Disease coding in claims databases may reflect financial incentives for reimbursement rather than clinically verified definitions, increasing the potential for misclassification of exposure and bias towards the null; however, we believe this was balanced between cohorts. In addition, this study was not designed to assess causality and there are other variables that may influence the development of RSV infection, RW or asthma, eg, allergic diseases, that are generally under-reported in administrative claims data and hence were

not included in the multivariable analysis. Nevertheless, these results confirm that there is a strong association between the exposure and the outcome.

In conclusion, RSV infection represents a major burden on the US healthcare system due to significant acute and long-term respiratory morbidity. The present large population-based, real-world study shows that full-term Medicaid and commercially-insured children that had an RSV infection during the first year of life had a significant risk of developing RW or asthma during the first five years of life. Early RSV prevention or treatment may improve the outcomes in both low and high-risk infants and help reducing the burden of chronic pulmonary complications associated with RSV.

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Author Contribution:

Conception and design: AM, BW, NT, WC, EF, OR

Data analysis and interpretation: AM, BW, RV, OR

Manuscript writing: All authors

Final approval of manuscript: All authors

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References: (32/30)

1. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*. 2010;375(9725):1545-1555.
2. Silvestri M, Marando F, Costanzo AM, di Luzio Paparatti U, Rossi GA. Respiratory Syncytial Virus-associated hospitalization in premature infants who did not receive palivizumab prophylaxis in Italy: a retrospective analysis from the Osservatorio Study. *Ital J Pediatr*. 2016;42:40.
3. Stein RT, Bont LJ, Zar H, et al. Respiratory syncytial virus hospitalization and mortality: Systematic review and meta-analysis. *Pediatr Pulmonol*. 2017;52(4):556-569.
4. 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.
5. Stockman LJ, Curns AT, Anderson LJ, Fischer-Langley G. Respiratory syncytial virus-associated hospitalizations among infants and young children in the United States, 1997-2006. *Pediatr Infect Dis J*. 2012;31(1):5-9.
6. Centres for Disease Control and Prevention. Asthma in children. 2018; <https://www.cdc.gov/vitalsigns/childhood-asthma/index.html>. Accessed July 23, 2018.
7. Fauroux B, Simoes 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(2):173-197.
8. Carroll KN, Wu P, Gebretsadik T, et al. Season of infant bronchiolitis and estimates of subsequent risk and burden of early childhood asthma. *J Allergy Clin Immunol*. 2009;123(4):964-966.
9. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. *BMC Pediatr*. 2013;13:97.
10. Escobar GJ, Ragins A, Li SX, Prager L, Masaquel AS, Kipnis P. Recurrent wheezing in the third year of life among children born at 32 weeks' gestation or later: relationship to laboratory-confirmed, medically attended infection with respiratory syncytial virus during the first year of life. *Arch Pediatr Adolesc Med*. 2010;164(10):915-922.

- Accepted Article
11. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet*. 1999;354(9178):541-545.
 12. Bacharier LB, Cohen R, Schweiger T, et al. Determinants of asthma after severe respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol*. 2012;130(1):91-100 e103.
 13. Carroll KN, Wu P, Gebretsadik T, et al. The severity-dependent relationship of infant bronchiolitis on the risk and morbidity of early childhood asthma. *J Allergy Clin Immunol*. 2009;123(5):1055-1061, 1061 e1051.
 14. 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(5):386-392.
 15. Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. *Pediatr Pulmonol*. 2004;38(2):155-160.
 16. Kusel MM, de Klerk NH, Keadze T, et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol*. 2007;119(5):1105-1110.
 17. Murray M, Webb MS, O'Callaghan C, Swarbrick AS, Milner AD. Respiratory status and allergy after bronchiolitis. *Arch Dis Child*. 1992;67(4):482-487.
 18. Noble V, Murray M, Webb MS, Alexander J, Swarbrick AS, Milner AD. Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child*. 1997;76(4):315-319.
 19. Ruotsalainen M, Hyvarinen MK, Piippo-Savolainen E, Korppi M. Adolescent asthma after rhinovirus and respiratory syncytial virus bronchiolitis. *Pediatr Pulmonol*. 2013;48(7):633-639.
 20. Ruotsalainen M, Piippo-Savolainen E, Hyvarinen MK, Korppi M. Respiratory morbidity in adulthood after respiratory syncytial virus hospitalization in infancy. *Pediatr Infect Dis J*. 2010;29(9):872-874.
 21. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med*. 2000;161(5):1501-1507.

- Accepted Article
22. Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171(2):137-141.
 23. Wu P, Dupont WD, Griffin MR, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. *Am J Respir Crit Care Med*. 2008;178(11):1123-1129.
 24. Homaira N, Briggs N, Pardy C, et al. Association between respiratory syncytial viral disease and the subsequent risk of the first episode of severe asthma in different subgroups of high-risk Australian children: a whole-of-population-based cohort study. *BMJ Open*. 2017;7(11):e017936.
 25. Simoes EAF, Chirikov V, Botteman M, Kwon Y, Kuznik A. Long-Term Assessment of Healthcare Utilization Five Years After Respiratory Syncytial Virus Infection in US Infants. *J Infect Dis*. 2019.
 26. James KM, Gebretsadik T, Escobar GJ, et al. Risk of childhood asthma following infant bronchiolitis during the respiratory syncytial virus season. *J Allergy Clin Immunol*. 2013;132(1):227-229.
 27. Rose EB, Wheatley A, Langley G, Gerber S, Haynes A. Respiratory Syncytial Virus Seasonality - United States, 2014-2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(2):71-76.
 28. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B, Bjorksten B. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics*. 1995;95(4):500-505.
 29. 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(12):1045-1052.
 30. Mejias A, Chavez-Bueno S, Rios AM, et al. Anti-respiratory syncytial virus (RSV) neutralizing antibody decreases lung inflammation, airway obstruction, and airway hyperresponsiveness in a murine RSV model. *Antimicrob Agents Chemother*. 2004;48(5):1811-1822.
 31. Mochizuki H, Kusuda S, Okada K, et al. Palivizumab Prophylaxis in Preterm Infants and Subsequent Recurrent Wheezing. Six-Year Follow-up Study. *Am J Respir Crit Care Med*. 2017;196(1):29-38.

32. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med*. 2013;368(19):1791-1799.

Figure Legends

Figure 1. Attrition

Figure 2. Event-free Survival and Probability Density of At-Risk Years

Footnote to figures

Footnote to figure 1

CCAE, Commercial Claims and Encounters database; MDCD, Medicaid; RSV, respiratory syncytial virus; SES, Socio-Economic Status

^aIdentification periods: CCAE, 1 January 2000 – 31 December 2015; MDCD, 1 January 2006 – 31 December 2015; Optum SES, 1 January 2006 – 30 September 2016.

^bRSV related conditions include: acute bronchitis due to RSV, acute bronchiolitis due to other infectious organisms, unspecified viral pneumonia, bronchopneumonia organism unspecified, and pneumonia, organism unspecified

^cDefined as infants without any diagnosis for short gestation (<37 weeks), low birth weight (<2,500 grams), slow fetal growth and malnutrition, congenital heart disease, congenital lung disease, and wheezing or asthma during the first year of life. Non-RSV infants were excluded if hospitalized for any reason after their birth discharge during the first year.

^dReflects percentage of patients in the corresponding cohort in Step 4. N's represent matched pairs

Footnote to figure 2

CCAE, Commercial Claims and Encounters database; MDCD, Medicaid; RSV, respiratory syncytial virus; SES, Socio-Economic Status; aHR, adjusted hazard ratio; RSV, respiratory syncytial virus

Table 1. Demographics of Matched RSV/Non-RSV Cohorts with 1-2 Years of Follow-up Data

	Truven Commercial RSV/Non-RSV		Truven Medicaid RSV/Non-RSV		Optum SES RSV/Non-RSV	
Sample size per cohort	38,494		62,846		23,099	
Female (n, %)	17,606	45.7%	30,107	47.9%	10,692	46.3%
Year of birth (n, %)						
2000-2005	6,155	16.0%	n/a	n/a	n/a	n/a
2006	2,551	6.6%	3,661	5.8%	2,267	9.8%
2007	3,126	8.1%	4,503	7.2%	2,586	11.2%
2008	3,370	8.8%	5,710	9.1%	2,620	11.3%
2009	4,008	10.4%	6,162	9.8%	2,612	11.3%
2010	4,844	12.6%	5,321	8.5%	2,555	11.1%
2011	3,769	9.8%	6,460	10.3%	2,507	10.9%
2012	4,360	11.3%	11,705	18.6%	2,459	10.6%
2013	3,214	8.3%	9,678	15.4%	2,013	8.7%
2014	3,097	8.0%	9,646	15.3%	1,979	8.6%
Month of Birth (n, %)						
January	2,494	6.5%	4,819	7.7%	788	3.4%
February	2,263	5.9%	4,017	6.4%	1,556	6.7%
March	2,552	6.6%	4,219	6.7%	1,448	6.3%
April	2,882	7.5%	4,115	6.5%	1,791	7.8%
May	2,945	7.7%	4,490	7.1%	1,813	7.8%
June	3,119	8.1%	5,060	8.1%	1,983	8.6%
July	3,851	10.0%	5,624	8.9%	2,273	9.8%
August	3,844	10.0%	6,200	9.9%	2,282	9.9%
September	3,904	10.1%	6,191	9.9%	2,622	11.4%
October	4,094	10.6%	6,323	10.1%	2,486	10.8%
November	3,478	9.0%	6,109	9.7%	2,149	9.3%
December	3,068	8.0%	5,679	9.0%	1,908	8.3%
Region (n, %)						
Northeast	4,527	11.8%	n/a	n/a	1,952	8.5%
Midwest	8,194	21.3%	n/a	n/a	5,295	22.9%

South	20,981	54.5%	n/a	n/a	12,155	52.6%
West	4,338	11.3%	n/a	n/a	3,641	15.8%
Other	454	1.2%	n/a	n/a	56	0.2%
Plan Type (n, %)						
HMO	6,412	16.7%	45,302	72.1%	2,115	9.2%
PPO	23,590	61.3%	23	0.0%	997	4.3%
POS	3,268	8.5%	n/a	n/a	16,379	70.9%
OTH	4,782	12.4%	17,521	27.9%	3,608	15.6%
Follow-up (n, %)						
1-2 years	38,494	100.0%	62,846	100.0%	23,099	100.0%
2-3 years	25,603	66.5%	41,836	66.6%	15,641	67.7%
3-4 years	17,429	45.3%	28,332	45.1%	10,739	46.5%
4-5 years	11,921	31.0%	17,465	27.8%	7,411	32.1%

HMO, health maintenance organization; PPO, preferred provider organization; POS, point of service; RSV, respiratory syncytial virus; SES, Socio-Economic Status

Table 2. Baseline Characteristics of the Matched RSV/Non-RSV Cohorts with 1-2 Years of Follow-up Data

	Truven Commercial			Truven Medicaid			Optum SES		
	RSV	Non- RSV	<i>p</i> -value	RSV	Non- RSV	<i>p</i> -value	RSV	Non- RSV	<i>p</i> -value
Sample Size, n	38,494	38,494		62,846	62,846		23,099	23,099	
Length of hospitalization, mean (SD)	3.9 (3.8)	2.0 (1.8)	<.0001	5.9 (5.0)	2.6 (1.8)	.02	2.9 (3.8)	1.4 (1.8)	<.0001
Comorbid conditions, %						<.0001			
Bronchopulmonary dysplasia	0.03%	0.00%	.07	0.04%	0.02%	.59	0.03%	0.01%	.29
Congestive heart failure	0.08%	0.01%	<.0001	0.12%	0.01%	.13	0.11%	0.01%	<.0001
Cystic Fibrosis	0.07%	0.03%	.01	0.05%	0.04%	<.0001	0.06%	0.05%	.55
Down's syndrome	0.15%	0.04%	<.0001	0.15%	0.12%	<.0001	0.17%	0.03%	<.0001
Infant respiratory distress syndrome	1.44%	0.43%	<.0001	1.32%	0.42%	<.0001	1.12%	0.41%	<.0001
Infections specific to the perinatal period	5.43%	3.24%	<.0001	9.70%	5.09%	.01	5.94%	3.74%	<.0001
Immunodeficiency	0.13%	0.02%	<.0001	0.10%	0.03%	<.0001	0.17%	0.03%	<.0001
Neuromuscular disease	0.04%	0.01%	.22	0.03%	0.01%	<.0001	0.05%	0.01%	.01
Other respiratory conditions of fetus and newborn	5.82%	2.57%	<.0001	7.73%	3.44%	.02	4.90%	2.24%	<.0001
Primary pulmonary hypertension	0.03%	0.00%	.00	0.04%	0.01%	<.0001	0.03%	0.02%	.37
Medical Interventions in the first year, %									
Influenza vaccination	38.17%	36.06%	<.0001	25.03%	23.35%	<.0001	41.83%	39.67%	<.0001
Pneumococcal vaccination	89.41%	84.56%	<.0001	79.24%	72.01%	<.0001	95.25%	91.38%	<.0001
Antibiotics	76.71%	44.71%	<.0001	76.30%	39.60%	<.0001	74.50%	41.04%	<.0001
Chronic systemic corticosteroid therapy*	24.77%	5.44%	<.0001	30.01%	4.85%	<.0001	21.34%	4.74%	<.0001
Inhaled corticosteroid therapy	8.70%	0.34%	<.0001	8.82%	0.35%	<.0001	6.37%	0.24%	<.0001
Other recurrent wheezing/ asthma risk factors, %									
NICU stay (Level II)	2.02%	1.35%	<.0001	2.59%	1.84%	<.0001	0.12%	0.10%	.78

NICU stay (Level III)	1.88%	1.05%	<.0001	2.34%	1.53%	<.0001	0.06%	0.04%	.52
NICU stay (Level IV)	1.48%	0.71%	<.0001	1.64%	0.92%	<.0001	1.55%	1.13%	.0001
Presence of RSV test	45.19%	2.97%	<.0001	57.00%	3.41%	<.0001	54.30%	3.12%	<.0001
Presence of cannula procedure	0.08%	0.00%	<.0001	0.01%	0.00%	.04	0.07%	0.00%	<.0001
Use of continuous positive airway pressure	0.04%	0.00%	.0001	0.06%	0.00%	<.0001	0.04%	0.01%	.02
Use of long-term supplemental oxygen therapy	0.01%	0.00%	.25	0.01%	0.00%	.13	0.01%	0.00%	.25
Use of mechanical ventilation	0.02%	0.00%	.03	0.03%	0.00%	<.0001	0.03%	0.00%	.02

NICU, neonatal care unit; RSV, respiratory syncytial virus; SD, standard deviation; SES, Socio-Economic Status *Continuous systemic corticosteroid use for ≥ 14 days

Table 3. Cumulative Incidence

	RSV Cohort			Non-RSV Cohort			RSV vs. Non-RSV (reference)	
	Total # of Patients At-Risk	# of Cases	Cumulative Incidence	Total # of Patients At-Risk	# of Cases	Cumulative Incidence	Adj. OR (95% CI)	p-value
Truven Commercial								
1-2 years follow-up	38,494	6,773	17.6%	38,494	1,908	5.0%	4.1 (3.9, 4.4)	<.0001
1-3 years follow-up	25,603	5,468	21.4%	25,603	2,023	7.9%	3.2 (3.0, 3.3)	<.0001
1-4 years follow-up	17,429	4,146	23.8%	17,429	1,690	9.7%	2.9 (2.7, 3.1)	<.0001
1-5 years follow-up	11,921	3,004	25.2%	11,921	1,362	11.4%	2.6 (2.5, 2.9)	<.0001
Truven Medicaid								
1-2 years follow-up	62,846	8,682	13.8%	62,846	2,784	4.4%	3.5 (3.3, 3.6)	<.0001
1-3 years follow-up	41,836	9,334	22.3%	41,836	3,550	8.5%	3.1 (3.0, 3.2)	<.0001
1-4 years follow-up	28,332	8,087	28.5%	28,332	3,481	12.3%	2.9 (2.8, 3.0)	<.0001
1-5 years follow-up	17,465	6,178	35.4%	17,465	2,912	16.7%	2.8 (2.6, 2.9)	<.0001
Optum SES								
1-2 years follow-up	23,099	2,413	10.4%	23,099	796	3.4%	3.3 (3.0, 3.6)	<.0001
1-3 years follow-up	15,641	2,589	16.6%	15,641	1,018	6.5%	2.9 (2.6, 3.1)	<.0001
1-4 years follow-up	10,739	2,195	20.4%	10,739	1,069	10.0%	2.3 (2.1, 2.5)	<.0001
1-5 years follow-up	7,411	1,808	24.4%	7,411	944	12.7%	2.2 (2.0, 2.4)	<.0001

Adj, adjusted; CI, confidence interval; OR, odds ratio; RSV, respiratory syncytial virus; SES, Socio-Economic Status

Adjusted odds ratios were calculated via multivariable conditional logistic regression controlling for covariates including comorbid infections specific to the perinatal period or other respiratory conditions of fetus and newborn (yes/no), influenza vaccination (yes/no), and pneumococcal vaccination (yes/no)

Figure 1. Attrition

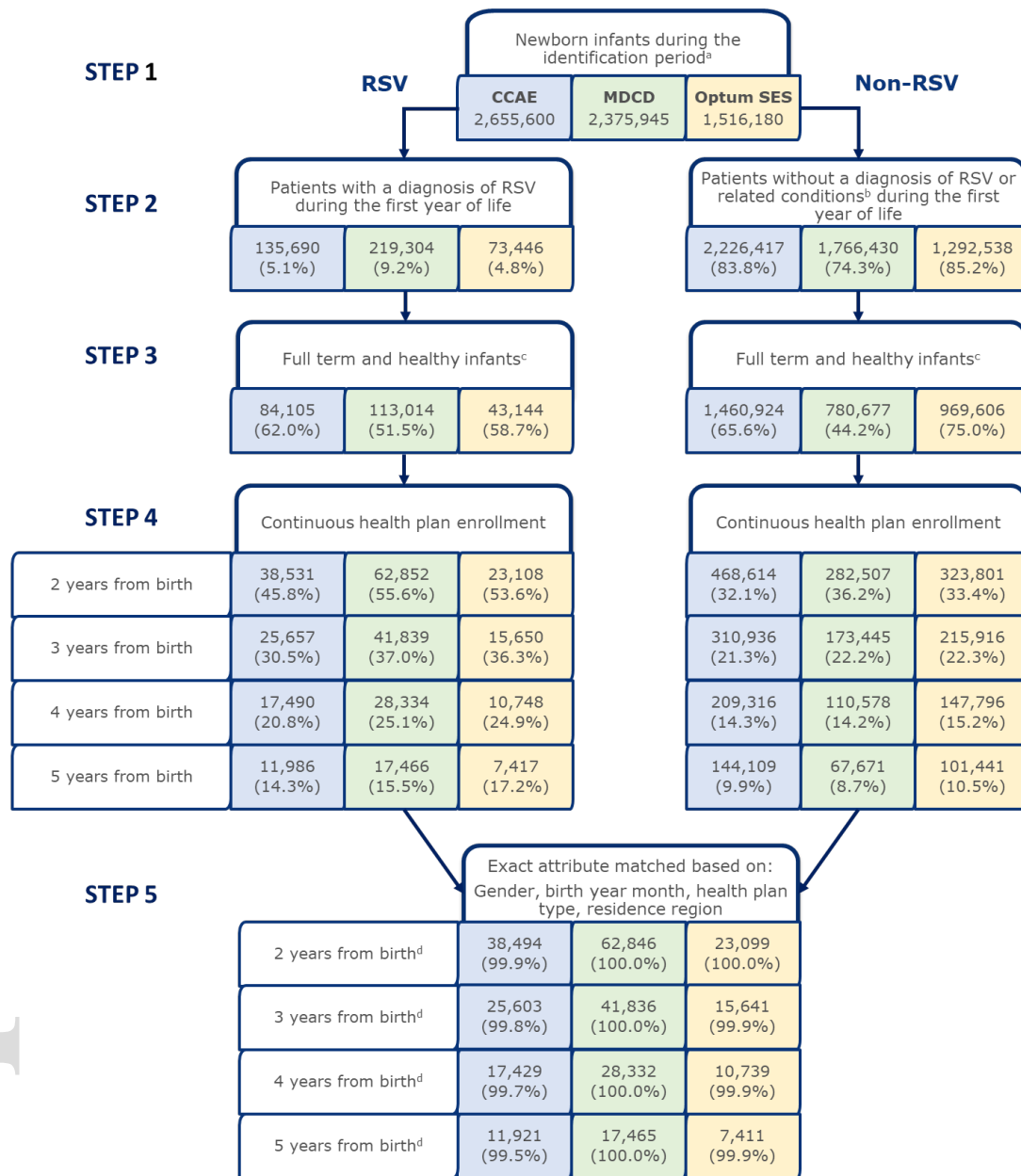
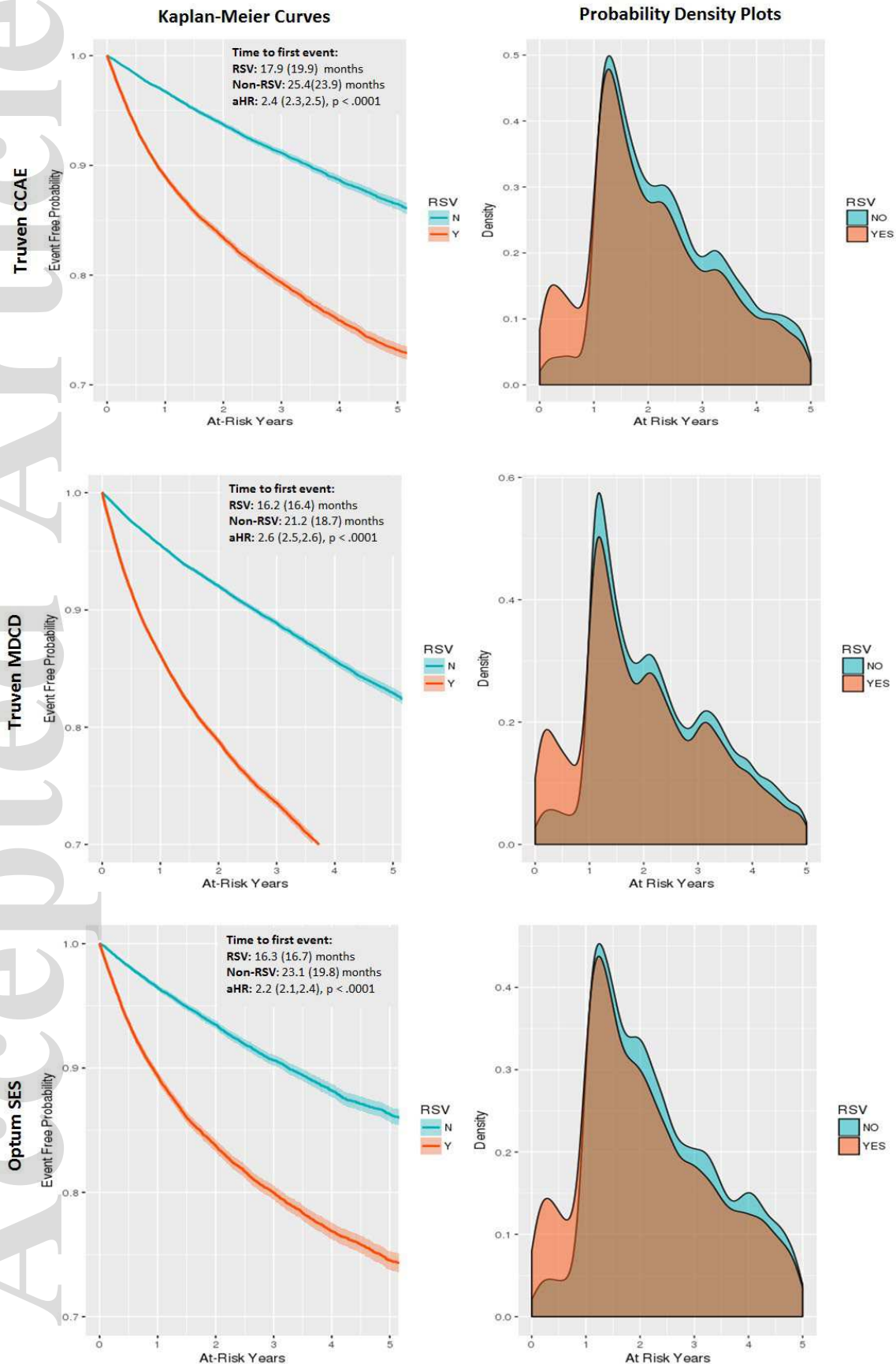
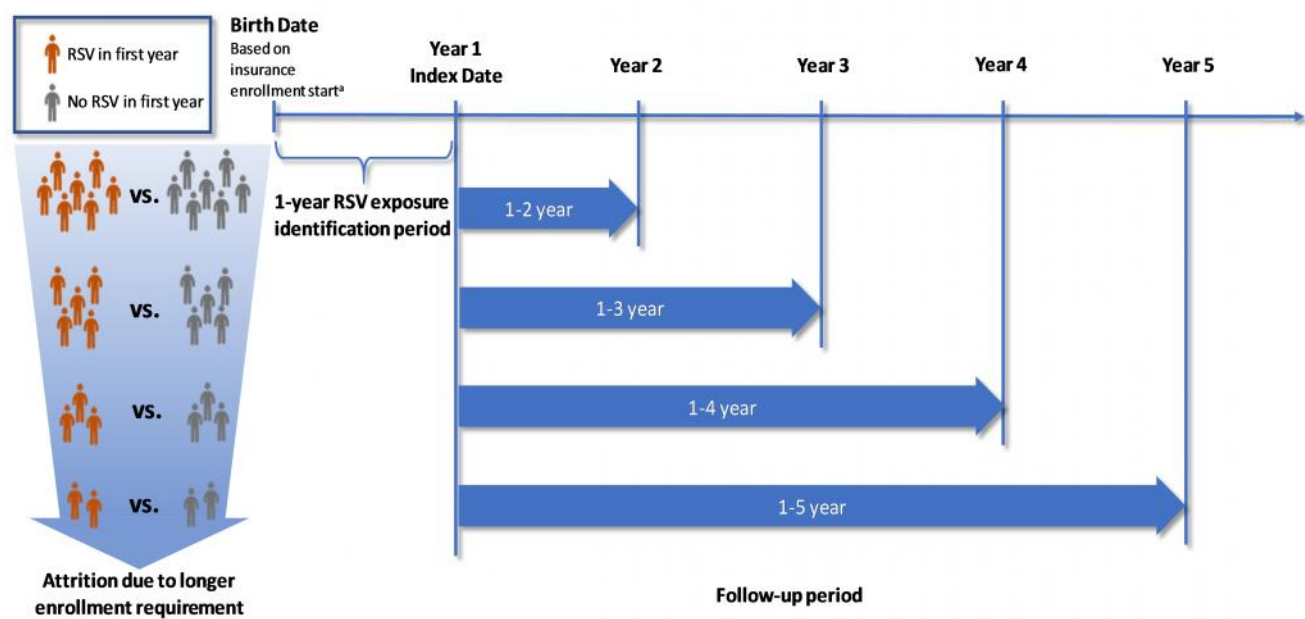


Figure 2. Event-free Survival and Probability Density of At-Risk Years

eFigure 1. Study Design



RSV: respiratory syncytial virus

^a Insurance companies generally assign the first day of the month as the newborn's birth date; therefore, claims databases do not include the infant's actual date of birth. Thus, the difference between the assigned and actual dates can be up to 30 days, with an average difference of approximately 15 days.

Online only material

eTable 1: Codes used for data extraction for various diagnoses, medications and procedures

Diagnoses		
	ICD-9-CM Diagnosis Code	ICD-10-CM Diagnosis Code
RSV	79.60%*	B97.4%,
Acute bronchiolitis due to RSV	466.11	J21.0%
Pneumonia due to RSV	480.10%	J12.1%
Acute bronchitis due to RSV	466.0%	J20.5%
Acute bronchiolitis due to other infectious organisms	466.19	J21.1%, J21.8%, J21.9%
Unspecified viral pneumonia	480.9%	J12.9%
Bronchopneumonia organism unspecified	485.%	J18.0%
Pneumonia, organism unspecified	486.%	J18.8%, J18.9%
Influenza or bacterial pneumonia	481.%, 482.%, 487.%	J13.%, J14.%, J15.0%, J15.6%, J15.8%, J15.9%, A48.1%, J10.%, J11.%
Asthma	493.%, 506.3%	J45.%, J68.3%
Wheezing	786.07	R06.2%
Short gestation (defined as <37 completed weeks of gestation)	765.20 - 765.28	P07.2%, P07.3%
Low birth weight (<2500 grams)	765.0%, 765.1%	P07.0%, P07.1%
Slow fetal growth and malnutrition	764.%	P05.%
Congenital heart disease (CHD)	746.%	Q24.%
Congenital lung disease or anomalies of	748.%	Q30.% - Q34.%

respiratory system		
Bronchopulmonary dysplasia (BPD)	770.7%	P27.%
Congestive heart failure	428.%	I50.%
Cystic fibrosis	277.0%	E84.%
Down's syndrome	758.0%	Q90.%
Infant respiratory distress syndrome (RDS)	769.%	P22.%
Infections specific to the perinatal period	771.%	P35.% - P39.%
Immunodeficiency	279.%	D80.% - D89.%
Other respiratory conditions of fetus and newborn	770.%	P23.% - P28.%
Neuromuscular disease	358.%	G70.%
Primary pulmonary hypertension	416.0%	I27.0%
Long-term supplemental oxygen therapy	V46.2%	Z99.81%
Medications and procedures		
	GPI code	CPT/HCPCS Code
Prophylaxis use of palivizumab	19502060%	S9562, C9003
Influenza vaccination	17100020%	90470, 90653-90664, 90666-90668, G9141, G9142, Q2034-Q2039
Pneumococcal vaccination	17200065%	90669, 90670, 90732
Angiotensin-converting enzyme (ACE) inhibitors	3610%, 369915%, 369918%, 369985%	
Angiotensin receptor blockers (ARB)	3615%, 369927%, 369930%, 369940%, 369945%, 409920%	
Antianginal medications	32%	
Antibiotics	01%-08%, 1600%- 1629%, 1699%	J0290, J0295, J2543, S0040, J0690, J1890, S0074, J0694, J0697, S0021, J0698, J0713, J0715, J0696, J0692, J0712, S0077, J2010, J1364, J0456, J2460, J2265, J0120, J0200, J0744, J1956, J2280, S0034, J1590, J0278, J1580, J1840, J1850, J3000, J3260, S0073, J0770, J1267,

Antihypertensive medications	36%	C9241, J1335, J2185, J3243, J0743, S0039
Beta blockers	33%, 369920%, 369927%, 369988%	J0210, J2760, J0360, S0139, J1730, J2670 J1800, C9482
Cardiotonic medications	31%	J2260, J1160, J1162
Chronic corticosteroid therapy (defined as ≥180 days of total length of therapy)	22%, 8915%	J0702, J7624, J7622, J7633, J7627, J7634, J7626, J8540, J1094, J1100, J7312, J7637, J7638, J1700, J1710, J1720, J1020, J2030, J1040, J2920, J2930, J7509, J2650, J7510, J7506, J7512, J3300, J3301, J3302, J3303, J7683, J7684
Diuretic medications	37%, 369918%, 369920%, 369940%, 369945%, 369950%, 369955%, 369960%, 369968%, 369990%	J1120, S0171, J1940, J3265, J2150, J7665, J3350, J1205
Other cardiovascular agents	40%	J2440, S0090, J1325, S0155, Q4074, J3285, J7686, J2325, J0270, J0275
Vasopressor	38%	J1250, J1265, J0171, 70, C9447
RSV test		87807, 87280, 87420, 87631, 87632, 87633
Cannula procedure		33951, 33953, 33955, 33957, 33959, 33963, 33965, 33969, 33985, A4615, A4623
Continuous positive airway pressure (CPAP)		94660
Long-term supplemental oxygen therapy		4030F, E0424, E0444, E1390, E1392, K0738, S8120, S8121
Mechanical ventilation		94002, 94003
UB-92 Rev codes		
Neonatal Intensive Care Unit (NICU)	017%	
ICU (including CCU)	020%, 021	

Abbreviations: GPI, Generic Product Identifier; CPT, Current Procedural Terminology; HCPCS, The Healthcare Common Procedure Coding System; UB, Uniform/Universal Billing

*% sign was used as a wildcard for data retrieval, it denotes that all sub-codes under the "parent" codes were included in the analysis.

eTable 2. Incidence Rate Per 1,000 Patient-Years (in original cohorts)

	RSV	Non-RSV	RSV vs. Non-RSV (reference)	
			Adj. IRR (95% CI)	p-value
Truven Commercial				
Total # of patients at-risk	38,494	38,494		
# of incident cases	8,005	3,612		
Total patient-years at-risk	114,833	126,005		
Incident rate per 1,000 patient-years	69.7	28.7	2.4 (2.3, 2.5)	<.0001
Truven Medicaid				
Total # of patients at-risk	62,846	62,846		
# of incident cases	16,161	6,851		
Total patient-years at-risk	161,352	178,109		
Incident rate per 1,000 patient-years	100.2	38.5	2.6 (2.5, 2.7)	<.0001
Optum SES				
Total # of patients at-risk	23,099	23,099		
# of incident cases	4,561	2,210		
Total patient-years at-risk	66,134	73,056		
Incident rate per 1,000 patient-years	69.0	30.3	2.3 (2.2, 2.4)	<.0001

Abbreviations: Adj. IRR, adjusted incidence rate ratio; CI, confidence interval; RSV, respiratory syncytial virus; SES, Socio-Economic Status

eTable 3 Cumulative Incidence (Excluding Infants with Any Comorbid Condition Reported in Table 2)

	RSV Cohort			Non-RSV Cohort			RSV vs. Non-RSV (reference)	
	Total # of Patients At-Risk	# of Cases	Cumulative Incidence	Total # of Patients At-Risk	# of Cases	Cumulative Incidence	Adj. OR (95% CI)	p-value
Truven Commercial								
1–2 years follow-up	32,280	5,615	17.4%	32,280	1,569	4.9%	4.2 (3.9, 4.4)	<.0001
1–3 years follow-up	21,446	4,559	21.3%	21,446	1,678	7.8%	3.2 (3.0, 3.4)	<.0001
1–4 years follow-up	14,652	3,453	23.6%	14,652	1,386	9.5%	3.0 (2.8, 3.2)	<.0001
1–5 years follow-up	10,003	2,517	25.2%	10,003	1,143	11.4%	2.6 (2.4, 2.9)	<.0001
Truven Medicaid								
1–2 years follow-up	48,173	6,490	13.5%	48,173	2,115	4.4%	3.4 (3.2, 3.6)	<.0001
1–3 years follow-up	31,866	6,961	21.8%	31,866	2,676	8.4%	3.1 (2.9, 3.2)	<.0001
1–4 years follow-up	21,654	6,032	27.9%	21,654	2,556	11.8%	3.0 (2.8, 3.1)	<.0001
1–5 years follow-up	13,346	4,622	34.6%	13,346	2,197	16.5%	2.7 (2.6, 2.9)	<.0001
Optum SES								
1–2 years follow-up	19,411	1,975	10.2%	19,411	677	3.5%	3.2 (2.9, 3.5)	<.0001
1–3 years follow-up	13,082	2,073	15.8%	13,082	821	6.3%	2.8 (2.6, 3.0)	<.0001
1–4 years follow-up	8,988	1,783	19.8%	8,988	880	9.8%	2.3 (2.1, 2.5)	<.0001
1–5 years follow-up	6,190	1,477	23.9%	6,190	774	12.5%	2.2 (2.0, 2.4)	<.0001

Abbreviations: Adj, adjusted; CI, confidence interval; OR, odds ratio; RSV, respiratory syncytial virus

Adjusted odds ratios were calculated via multivariable conditional logistic regression controlling for covariates including comorbid with infections specific to the perinatal period or other respiratory conditions of fetus and newborn (yes/no), influenza vaccination (yes/no), and pneumococcal vaccination (yes/no).

Population Restrictions: Excluded Cases and Controls with the following comorbidities: Bronchopulmonary dysplasia, Congestive heart failure, Cystic fibrosis, Down's syndrome, Infant respiratory distress syndrome, Infections specific to the perinatal period, Immunodeficiency, Neuromuscular disease, Other respiratory conditions of fetus and newborn, Primary pulmonary hypertension

eTable 4. Incidence Rate Per 1,000 Patient-Years (Excluding infants with any comorbid condition reported in Table 2)

	RSV	Non-RSV	RSV vs. Non-RSV (reference)	
			Adj. IRR (95% CI)	p-value
Truven Commercial				
Total # of patients at-risk	32,280	32,280		
# of incident cases	6,643	2,998		
Total patient-years at-risk	96,404	105,840		
Incident rate per 1,000 patient-years	68.9	28.3	2.42 (2.31, 2.53)	<.0001
Truven Medicaid				
Total # of patients at-risk	48,173	48,173		
# of incident cases	12,111	5,214		
Total patient-years at-risk	124,552	136,590		
Incident rate per 1,000 patient-years	97.2	38.2	2.54 (2.46, 2.63)	<.0001
Optum SES				
Total # of patients at-risk	19,411	19,411		
# of incident cases	3,750	1,851		
Total patient-years at-risk	55,725	61,213		
Incident rate per 1,000 patient-years	67.3	30.2	2.22 (2.09, 2.34)	<.0001

Abbreviations: Adj. IRR, adjusted incidence rate ratio; CI, confidence interval; RSV, respiratory syncytial virus

Population Restrictions: Excluded Cases and Controls with the following: Bronchopulmonary dysplasia, Congestive heart failure, Cystic fibrosis, Down's syndrome, Infant respiratory distress syndrome, Infections specific to the perinatal period, Immunodeficiency, Neuromuscular disease, Other respiratory conditions of fetus and newborn, Primary pulmonary hypertension