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Incidence and economic burden of respiratory syncytial virus among adults in the United States: A retrospective analysis using 2 insurance claims databases

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Plain language summary

The risk of acquiring respiratory syncytial virus (RSV) infection is higher among patients aged 60 years or older and among individuals with preexisting medical conditions affecting their lungs, heart, and immune system. Medical costs related to RSV infection are substantial; they increase in the week before RSV diagnosis and peak during the week after diagnosis. Medical costs are highest among patients aged 60 years or older and those aged 18-59 years with preexisting conditions.

Implications for managed care pharmacy

The substantial burden of RSV highlights the need to raise awareness on the consequences of RSV infection, particularly among older and high-risk individuals. In addition to the development and implementation of rapid and inexpensive diagnostic testing and RSV-specific treatments, prophylactic RSV vaccines currently under investigation may also potentially benefit adults. Accompanying policies would need to be considered to optimize vaccine uptake, particularly among those at risk of serious outcomes such as respiratory failure and death.

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ABSTRACT

BACKGROUND: Respiratory syncytial virus (RSV) is a common, contagious, and seasonal pathogen causing 64 million acute respiratory infections annually in adults and children worldwide. High-risk adults, including older adults and those with cardiopulmonary conditions or weakened immune systems, are more likely to be infected. However, limited information exists on RSV incidence and associated costs among adults, including high-risk patients.

OBJECTIVE: To evaluate the annual incidence of medically attended, International Classification of Diseases (ICD)-coded RSV

among commercially insured adults and assess health care costs among adults with ICD-coded RSV in the United States.

METHODS: Optum's deidentified Clinformatics Data Mart Database (January 01, 2007, to June 30, 2020) and IBM's MarketScan Databases (January 01, 2000, to July 31, 2020) were used. Medically attended, ICD-coded RSV incidence among adults was assessed from July 1 of a given year to June 30 of the next year and reported per 100,000 population. Trends in all-cause mean weekly costs pre-RSV and post-RSV diagnosis were reported. Results were reported overall and among patients aged 60-64 years, 65 years or older, 85 years or older, and 18-59 years

at high risk of severe RSV (defined as having cardiopulmonary conditions or a weakened immune system).

RESULTS: Annual incidence of medically attended, ICD-coded RSV in adults overall was 22.0-52.9 in Optum and 23.4-63.6 in MarketScan. Incidence rates were higher among patients aged 60-64 years (Optum: 25.2-66.1; MarketScan: 31.9-82.1), 65 years or older (Optum: 37.3-75.5; MarketScan: 54.1-97.3), 85 years or older (Optum: 92.4-140.6; MarketScan: 79.4-234.7), and 18-59 years at high risk of severe RSV (Optum: 41.3-135.9; MarketScan: 46.3-112.4). Mean weekly costs increased during the week before (Optum: \$2,325; MarketScan: \$2,080) and post-RSV

diagnosis (Optum: \$9,523; MarketScan: \$3,551), compared with those in weeks 2-8 pre-RSV diagnosis (Optum: \$1,350; MarketScan: \$872). The increases in mean weekly costs during the week before and the week following RSV diagnosis were higher among patients aged 60-64 years (mean weekly costs in weeks 2-8 pre-RSV, week 1 pre-RSV, week 1 post-RSV; Optum: \$1,623, \$2,690, \$10,823; MarketScan: \$1,259, \$2,992, \$5,069), 65 years or older (Optum: \$1,731, \$3,067, \$12,866; MarketScan: \$1,517, \$3,571, \$5,268), 85 years or older (Optum: \$1,563, \$2,430, \$18,134; MarketScan: \$1,613, \$4,113, \$6,231), and 18-59 years at high risk of severe RSV (only for MarketScan: \$1,237, \$3,294, \$5,531; costs were similar for Optum).

CONCLUSIONS: Incidence of medically attended, ICD-coded RSV in adults was 22.0-63.6 per 100,000 population, a likely underestimation since RSV was not systematically tested and only RSV-coded cases were observed. Incremental costs associated with RSV were substantial. Incidence rates and costs were higher among patients aged 60 years or older and patients at high risk of severe RSV.

Respiratory syncytial virus (RSV) is a common, contagious, and seasonal pathogen that causes 64 million acute respiratory infections annually in adults and children worldwide.¹ RSV symptoms range from mild cold-/flu-like symptoms (eg, nasal congestion, cough, low-grade fever) to severe and potentially life-threatening symptoms (eg, acute bronchitis, pneumonia).²⁻⁵ Although initially recognized as a respiratory illness affecting pediatric populations, RSV also results in morbidity and mortality in adults, particularly among older adults.⁶ Based on estimates from the Centers for Disease Control and Prevention (CDC), more than 177,000 older adult patients are hospitalized each year in the United States because of RSV, and of these, approximately 14,000 die from the disease.⁷ In general, older adult patients with RSV have a 3- to 5-fold higher rate of hospitalizations and longer lengths of stays, in addition to twice as many emergency department (ED) and outpatient visits, as adults aged 18-49 years with RSV.⁸ For patients with chronic conditions, such as congestive heart failure, asthma, and chronic obstructive pulmonary disease (COPD), RSV symptoms are generally more severe.⁷

Although an RSV diagnosis may be established through laboratory tests (eg, reverse transcription polymerase chain reaction [RT-PCR], rapid antigen tests, and serology), testing is not routinely performed partly because it is not widely available.⁹ Additionally, given the highly similar clinical presentations of RSV and influenza infections, RSV is infrequently considered by physicians in the differential diagnosis of adult patients with influenza-like illnesses¹⁰ and is, therefore, not specifically tested. Even for patients with positive test results, current treatments for adults with RSV

are only supportive (eg, supplemental fluids and oxygen),¹¹ as there is no RSV-specific treatment available. Meanwhile, clinical studies on prophylactic RSV vaccines for adults are underway, but none have been approved to date.¹² The lack of widely available testing, limited physician awareness, and treatment and prophylactic options emphasize the challenges in RSV prevention and management among adults.

Information on RSV incidence and its clinical and economic burden among US adults is limited, as most prior studies have focused on infants and young children.¹³⁻¹⁶ Existing studies among adults^{6,17-21} generally evaluated RSV incidence only over a few winter seasons and most were not accompanied by detailed analyses of weekly health care costs or did not include high-risk patient subgroups. Given the limitations of available data and the potentially life-threatening consequences of RSV, especially among older and high-risk adults, there is a need to better understand the current burden of illness of RSV, including trends in incidence among specific patient subgroups and health care costs in the weeks preceding and following RSV infection. This knowledge could provide important insight into the potential impact of new prophylactic and treatment options for RSV in adults. Hence, this real-world study aimed to evaluate the annual incidence of medically attended, International Classification of Diseases (ICD)-coded RSV among commercially insured adults; describe the characteristics of patients with medically attended, ICD-coded RSV in the United States; and assess their health care costs. The analysis was stratified by age and patients at increased risk of developing RSV-related complications.

Methods

DATA SOURCE

To ensure that the analyses covered diverse populations and payer types, data from 2 deidentified US insurance claims databases were used: Optum's deidentified Clinformatics Data Mart Database (January 1, 2007, to June 30, 2020) and IBM's MarketScan Research Databases (January 1, 2000, to July 31, 2020).

The Optum data comprised both Commercial and Medicare Advantage health plan data, including medical and pharmacy claims, member eligibility, and estimated standard pricing (ie, estimated allowed amounts after applying standard pricing algorithms to account for pricing differences across health plans and provider contracts) for all claims. The MarketScan data included the Commercial Claims and Encounters database, the Medicare Supplemental and Coordination of Benefits database, and the Multi-State Medicaid Database. These

databases included claims for employees and their dependents, self-insured employers, Medicare-eligible retirees with employer-provided Medicare Supplemental plans, and Medicaid enrollees from multiple states. Medical services and prescription drug claims, as well as enrollment information, were included. Analyses were performed separately for both databases. Data were deidentified and comply with the patient requirements of the Health Insurance Portability and Accountability Act.

STUDY DESIGN

A cross-sectional study design was used for assessing the incidence of medically attended, ICD-coded RSV, identified using diagnosis codes observed in claims data (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]: 079.6, 466.11, and 480.1; *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM]: B97.4, J12.1, J20.5, and J21.0). The incidence of medically attended, ICD-coded RSV was assessed for each season, defined as the 1-year period starting from July 1 of a given year to June 30 of the next year, for the years available in each database (Optum: from 2007-2008 to 2019-2020; MarketScan: from 2000-2001 to 2019-2020).

A retrospective longitudinal study design was used to assess the economic burden of RSV. The index date was defined as the date of the first claim with an RSV ICD code (identified using the ICD-9-CM/ICD-10-CM codes listed above). The baseline period was defined as the 6 months pre-index and was used to capture patients' comorbidity profile and history of medication use. The observation period was defined as the time from the index date through the earliest of (1) 4 weeks after the index date (given the short duration of RSV infection), (2) end of continuous health plan eligibility, or (3) end of data availability. Sensitivity analyses were conducted to exclude the COVID-19 period (ie, from March 1, 2020, to end of data availability). Patients were included for the burden analysis if they had at least 1 claim with a recorded diagnosis of RSV, were aged 18 years or older as of the index date, and had at least 6 months of continuous insurance eligibility prior to the index date.

STUDY MEASURES

Annual incidence of RSV (ie, medically attended, ICD-coded RSV) for a given season was calculated by dividing the number of incident cases of RSV within that season (numerator) by the number of individuals with continuous insurance eligibility for the entire season and aged 18 years or older at the start of the season (denominator). Patients could be an incident case for more than 1 season if they

met the definition in more than 1 season; however, they could be considered an incident case only once per season, during the earliest month in which the patient met the definition for a given season.

For the analysis of the burden of RSV, demographic and clinical characteristics for patients with RSV were described during the 6-month baseline period. All-cause weekly health care costs were reported starting 8 weeks prior to the index date and for up to 4 weeks after the index date (ie, for patients who had <4 weeks of observation post-index [4.1% in Optum and 3.2% in MarketScan], costs were only evaluated during the weeks for which the patient was observed). This period was chosen since, based on preliminary explorations of the data, it was noted that weeks 2-8 pre-index represent baseline cost values that are relatively stable over time, whereas during weeks 2-4 post-index, costs stabilize again to the level of baseline cost values. The RSV index date was included in week 1 of the post-index period. Total all-cause health care costs reported were calculated as the sum of pharmacy and medical costs (sum of inpatient, outpatient, ER, and other service costs). Costs were reported in 2020 US dollars and adjusted using the medical care component of the US Consumer Price Index.

STATISTICAL ANALYSIS

Annual RSV incidence was reported per 100,000 population. To examine seasonality of medically attended, ICD-coded RSV infection, incidence rates were also assessed monthly within each season. Incidence rates were reported separately among patients aged ≥ 18 years or older, 60-64 years, 65 years or older, 85 years or older, and 18-59 years at high risk of severe RSV as of the start of the season of interest. Patients at high risk of severe RSV were identified based on the definition provided by the CDC⁷ and included those with a diagnosis for at least 1 of the following conditions pre-index: asthma, COPD, congestive heart failure, coronary artery disease, HIV/AIDS, or impaired immune system.

For the burden analysis, baseline characteristics were reported using means, SDs, and medians for continuous variables and counts and percentages for categorical variables. To evaluate the trends around the RSV-coded diagnosis, mean total health care costs were reported on a weekly basis before and after the index date. Baseline characteristics and health care costs were reported separately among patients aged 18 years or older, 60-64 years, 65 years or older, 85 years or older, and 18-59 years at high risk of severe RSV as of the index date. No formal statistical comparisons were made.

Results

RSV INCIDENCE

In Optum, the annual incidence of medically attended, ICD-coded RSV ranged from 22.0 to 52.9 per 100,000 population in adults. Incidence rates were higher among patients aged 60–64 years (25.2–66.1 per 100,000 population), 65 years or older (37.3–75.5 per 100,000 population), 85 years or older (92.4–140.6 per 100,000 population), and 18–59 years at high risk of severe RSV (41.3–135.9 per 100,000 population) ([Supplementary Table 1](#), available in online article).

In MarketScan, the annual incidence of medically attended, ICD-coded RSV ranged from 23.4 to 63.6 per 100,000 population in adults. Similar to Optum, incidence rates were higher among patients aged 60–64 years (31.9–82.1 per 100,000 population), 65 years or older (54.1–97.3 per 100,000 population), 85 years or older (79.2–234.7 per 100,000 population), and 18–59 years at high risk of severe RSV (46.3–112.4 per 100,000 population) ([Supplementary Table 2](#)).

In both Optum and MarketScan, incidence rates were lower in the summer months (June to August), increased in the fall (September to November), peaked in the winter months (December to February), and decreased again in the spring months (March to May) (Figure 1, [Supplementary Table 1](#), [Supplementary Table 2](#)). The seasonal trends of incidence rates were more pronounced among patients aged 65 years or older and 85 years or older, especially during more recent years.

CHARACTERISTICS OF PATIENTS WITH RSV

For the evaluation of the burden of RSV, a total of 36,000 adult patients with medically attended, ICD-coded RSV were identified in Optum ([Supplementary Figure 1A](#)), of which 2,622 (7.3%) were aged 60–64 years, 19,290 (53.6%) were aged 65 years or older, 3,294 (9.2%) were aged 85 years or older, and 5,059 (14.1%) were aged 18–59 years at high risk of severe RSV (Table 1). Overall, 60.1% of patients were female, 55.6% were covered by Medicare Advantage, and 44.4% were covered by commercial plans other than Medicare Advantage. On the index date, most adult patients had an RSV-related ICD code of acute bronchitis or acute bronchiolitis due to RSV (57.7%), with this proportion being smaller among patients aged 65 years or older (43.9%). The proportion of patients with pneumonia due to RSV was higher among older patients (29.2% among patients aged ≥65 years and 20.2% among patients aged ≥18 years). RSV was recorded during a hospitalization stay for 14.4% of patients. The mean baseline Quan-Charlson Comorbidity Index (Quan-CCI) score was 2.1 (SD=2.7) for patients aged 18 years or older and was higher for older adult patients;

25.0% had COPD, 18.2% had nonviral pneumonia, and 13.1% had bronchitis/bronchiolitis.

Among 81,861 patients with medically attended, ICD-coded RSV identified in the MarketScan database ([Supplementary Figure 1B](#)), 17,114 (20.9%) were aged 18–59 years at high risk of severe RSV; 8,049 (9.8%) were aged 60–64 years; 19,240 (23.5%) were aged 65 years or older; and 5,033 (6.1%) were aged 85 years or older (Table 1). Overall, 59.9% of the population were female, 64.9% were covered by commercial insurance plans, 21.1% by Medicare Supplemental plans only, 8.0% by Medicaid only (20.1% for patients aged 18–59 years at high risk of severe RSV), and 6.0% by both commercial and Medicare Supplemental plans. On the index date, most adult patients had an RSV-related diagnosis code of acute bronchitis or acute bronchiolitis due to RSV (71.7%); this proportion was smaller among patients aged 65 years or older (49.7%). Pneumonia due to RSV occurred in 15.7% of patients aged 18 years or older and increased to 38.9% among patients aged 65 years or older. RSV was recorded during a hospitalization stay for 12.6% of patients. The mean baseline Quan-CCI score was 1.1 (SD=1.9) among the adult population and was higher for older and high-risk patients; 12.8% had nonviral pneumonia, 12.1% had COPD, and 10.7% had bronchitis/bronchiolitis.

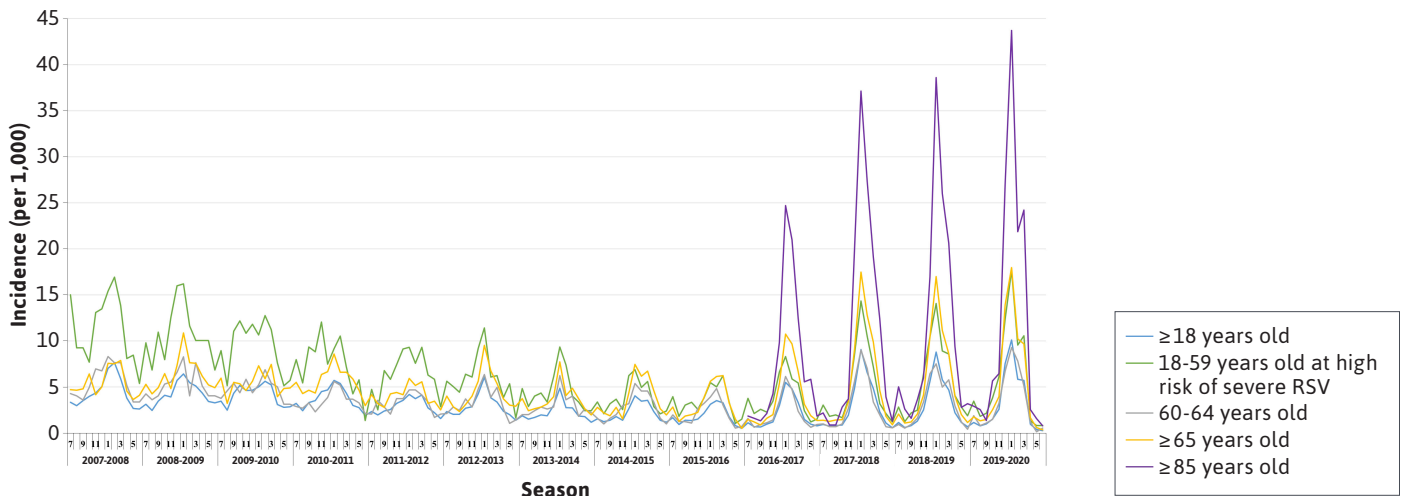
ECONOMIC BURDEN OF RSV

Overall, there was an increase in costs in the week before and after the index date of RSV in all populations. In Optum, the mean cost in weeks 2–8 pre-RSV were \$1,350. The mean weekly costs increased to \$2,325 during the week pre-RSV and to \$9,523 during the week following the ICD-coded RSV diagnosis (Figure 2A). Compared with the numbers for the overall adult RSV population, the increases in weekly costs during the week before and the week after the ICD-coded RSV diagnosis relative to weeks 2–8 pre-RSV were higher among patients aged 60–64 years (weeks 2–8 pre-RSV: \$1,623; week 1 pre-RSV: \$2,690; week 1 post-RSV: \$10,823), 65 years or older (\$1,731; \$3,067; \$12,866), and 85 years or older (\$1,563; \$2,430; \$18,134). For patients aged 18–59 years at high risk of severe RSV, weekly cost increases were similar to the general adult RSV population (\$1,668; \$2,537; \$9,330). Compared with costs in weeks 2–8 pre-RSV, costs were lower during weeks 2–4 after the ICD-coded RSV diagnosis in all patient groups (mean [median] follow-up time post-RSV: 3.9 [4.0] weeks; 4.1% with <4 weeks of follow-up).

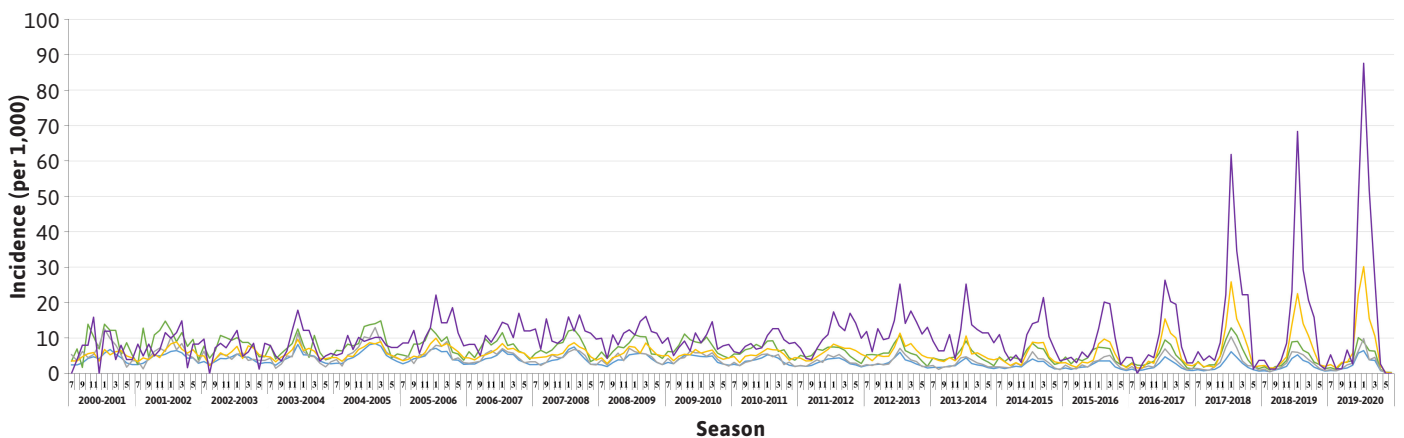
In MarketScan, the mean cost in weeks 2–8 pre-RSV diagnosis were \$872. The mean weekly costs increased to \$2,080 during the week pre-RSV and to \$3,551 during the week following the ICD-coded RSV diagnosis (Figure 2B). Compared with the numbers for the overall adult RSV population, the increases in weekly costs during the week

FIGURE 1 Monthly Incidence of Medically Attended, International Classification of Diseases–Coded RSV

A. Monthly incidence according to the Optum database



B. Monthly incidence according to the MarketScan database



Individuals included in the denominator for a given RSV season (July 1 to June 30) were aged 18 years on July 1 and had continuous insurance enrollment for the entire season. In Optum, dates of birth are set to a minimum of 1930; therefore, patients aged 85 years or older cannot be identified prior to the 2016-2017 season. Monthly incidence was calculated by evaluating the number of RSV infections in a given month, divided by the total number of eligible individuals within that season. If a patient has more than 1 RSV diagnosis in a season, the patient is only included in their first month of infection. Patients at high risk of severe RSV were defined as those with at least 1 diagnosis for 1 of the following conditions prior to the index date: asthma, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, HIV/AIDS, or impaired immune system. RSV=respiratory syncytial virus.

before and the week after the ICD-coded RSV diagnosis relative to weeks 2-8 pre-RSV were higher among patients aged 60-64 years (weeks 2-8 pre-RSV diagnosis: \$1,259; week 1 pre-RSV: \$2,992; week 1 post-RSV: \$5,069), 65 years or older (\$1,517; \$3,571; \$5,268), 85 years or older (\$1,613; \$4,113; \$6,231), and 18-59 years at high risk of severe RSV (\$1,237/\$3,294/\$5,531). Compared with costs in weeks 2-8

before RSV, costs were lower during weeks 2-4 after the ICD-coded RSV diagnosis in all patient groups (mean [median] follow-up time post-RSV: 3.9 [4.0] weeks; 3.2% with <4 weeks of follow-up).

The detailed breakdown of weekly costs in Optum and MarketScan (overall and by place of service) are shown in [Supplementary Table 3](#) and [Supplementary Table 4](#),

TABLE 1 Baseline Characteristics During the 6-Month Period Prior to the Index Date

	Aged ≥ 18 years	Aged 18-59 years at high risk of severe RSV ^a	Aged 60-64 years	Aged ≥ 65 years	Aged ≥ 85 years
Optum					
Sample size	36,000	5,059	2,622	19,290	3,294
Age group,^b n (%), years					
18-39	5,586 (15.5)	1,300 (25.7)	0 (0.0)	0 (0.0)	0 (0.0)
40-49	3,734 (10.4)	1,324 (26.2)	0 (0.0)	0 (0.0)	0 (0.0)
50-59	4,768 (13.2)	2,435 (48.1)	0 (0.0)	0 (0.0)	0 (0.0)
60-69	6,131 (17.0)	0 (0.0)	2,622 (100.0)	3,509 (18.2)	0 (0.0)
70-79	8,415 (23.4)	0 (0.0)	0 (0.0)	8,415 (43.6)	0 (0.0)
≥ 80	7,366 (20.5)	0 (0.0)	0 (0.0)	7,366 (38.2)	3,294 (100.0)
Female sex, n (%)	21,638 (60.1)	3,057 (60.4)	1,554 (59.3)	11,820 (61.3)	2,163 (65.7)
Year of index date,^b n (%)					
2007-2011	11,746 (32.6)	1,948 (38.5)	880 (33.6)	3,637 (18.9)	0 (0)
2012-2016	9,786 (27.2)	1,542 (30.5)	748 (28.5)	4,978 (25.8)	283 (8.6)
2017-2020	14,468 (40.2)	1,569 (31.0)	994 (37.9)	10,675 (55.3)	3,011 (91.4)
US geographic region, n (%)					
South	14,012 (38.9)	2,325 (46.0)	1,164 (44.4)	6,525 (33.8)	764 (23.2)
Northeast	7,516 (20.9)	1,064 (21.0)	454 (17.3)	4,262 (22.1)	796 (24.2)
West	7,251 (20.1)	787 (15.6)	508 (19.4)	4,119 (21.4)	794 (24.1)
Midwest	7,117 (19.8)	869 (17.2)	488 (18.6)	4,323 (22.4)	924 (28.1)
Unknown	104 (0.3)	14 (0.3)	8 (0.3)	61 (0.3)	16 (0.5)
Insurance plan/payer type, n (%)					
Commercial plans other than Medicare Advantage	15,990 (44.4)	4,021 (79.5)	1,660 (63.3)	1,571 (8.1)	110 (3.3)
Medicare Advantage	20,010 (55.6)	1,038 (20.5)	962 (36.7)	17,719 (91.9)	3,184 (96.7)
Index RSV diagnosis code, n (%)					
Pneumonia due to RSV	7,274 (20.2)	729 (14.4)	458 (17.5)	5,624 (29.2)	851 (25.8)
Acute bronchitis or acute bronchiolitis due to RSV	20,789 (57.7)	3,312 (65.5)	1,573 (60.0)	8,474 (43.9)	1,287 (39.1)
RSV or RSV as the cause of disease classified elsewhere	7,937 (22.0)	1,018 (20.1)	591 (22.5)	5,192 (26.9)	1,156 (35.1)
RSV recorded during hospitalization, n (%)	5,196 (14.4)	751 (14.8)	429 (16.4)	3,716 (19.3)	675 (20.5)
Quan-CCI, mean ± SD (median)	2.1 ± 2.7 (1.0)	1.7 ± 2.2 (1.0)	2.1 ± 2.7 (1.0)	3.1 ± 2.8 (2.0)	3.4 ± 2.6 (3.0)
Baseline respiratory-related conditions, n (%)					
Acute upper respiratory illness (eg, nasopharyngitis, sinusitis)	10,430 (29.0)	2,001 (39.6)	825 (31.5)	5,171 (26.8)	762 (23.1)
Chronic obstructive pulmonary disease	9,000 (25.0)	1,158 (22.9)	726 (27.7)	7,116 (36.9)	1,056 (32.1)
Pneumonia (nonviral)	6,565 (18.2)	848 (16.8)	454 (17.3)	5,001 (25.9)	767 (23.3)
Asthma	4,868 (13.5)	1,688 (33.4)	408 (15.6)	2,772 (14.4)	373 (11.3)
Bronchitis or bronchiolitis	4,711 (13.1)	903 (17.8)	401 (15.3)	2,704 (14.0)	388 (11.8)

continued on next page

TABLE 1 Baseline Characteristics During the 6-Month Period Prior to the Index Date (*continued*)

	Aged ≥ 18 years	Aged 18-59 years at high risk of severe RSV ^a	Aged 60-64 years	Aged ≥ 65 years	Aged ≥ 85 years
Baseline cardiovascular-related conditions, n (%)					
Hypertension	20,301 (56.4)	2,267 (44.8)	1,594 (60.8)	14,843 (76.9)	2,679 (81.3)
Coronary artery disease	8,025 (22.3)	821 (16.2)	531 (20.3)	6,673 (34.6)	1,253 (38.0)
Congestive heart failure	7,303 (20.3)	653 (12.9)	425 (16.2)	6,204 (32.2)	1,358 (41.2)
Baseline immune system disorders, n (%)					
Impaired immune system	964 (2.7)	392 (7.7)	131 (5.0)	441 (2.3)	34 (1.0)
HIV	153 (0.4)	102 (2.0)	11 (0.4)	37 (0.2)	4 (0.1)
Baseline diabetes, n (%)	9,836 (27.3)	1,183 (23.4)	871 (33.2)	7,080 (36.7)	965 (29.3)
MarketScan					
Sample size	81,861	17,114	8,049	19,240	5,033
Age group, n (%), years					
18-39	22,559 (27.6)	4,936 (28.8)	0 (0.0)	0 (0.0)	0 (0.0)
40-49	14,331 (17.5)	4,425 (25.9)	0 (0.0)	0 (0.0)	0 (0.0)
50-59	17,682 (21.6)	7,753 (45.3)	0 (0.0)	0 (0.0)	0 (0.0)
60-69	11,629 (14.2)	0 (0.0)	8,049 (100.0)	3,580 (18.6)	0 (0.0)
70-79	7,097 (8.7)	0 (0.0)	0 (0.0)	7,097 (36.9)	0 (0.0)
≥ 80	8,563 (10.5)	0 (0.0)	0 (0.0)	8,563 (44.5)	5,033 (100)
Female sex, n (%)	49,019 (59.9)	10,770 (62.9)	4,730 (58.8)	11,117 (57.8)	3,203 (63.6)
Year of index date, n (%)					
2000-2005	13,514 (16.5)	1,765 (10.3)	1,109 (13.8)	3,796 (19.7)	650 (12.9)
2006-2010	27,885 (34.1)	5,020 (29.3)	2,477 (30.8)	5,819 (30.2)	1,454 (28.9)
2011-2015	24,950 (30.5)	5,613 (32.8)	2,428 (30.2)	6,196 (32.2)	1,918 (38.1)
2016-2020	15,512 (18.9)	4,716 (27.6)	2,035 (25.3)	3,429 (17.8)	1,011 (20.1)
US geographic region, n (%)					
South	26,852 (32.8)	5,003 (29.2)	2,697 (33.5)	5,026 (26.1)	1,313 (26.1)
North Central	18,624 (22.8)	3,153 (18.4)	1,801 (22.4)	6,779 (35.2)	1,940 (38.5)
Northeast	16,198 (19.8)	3,241 (18.9)	1,704 (21.2)	4,514 (23.5)	1,207 (24.0)
West	13,234 (16.2)	2,171 (12.7)	1,247 (15.5)	2,685 (14.0)	544 (10.8)
Unknown	6,953 (8.5)	3,546 (20.7)	600 (7.5)	236 (1.2)	29 (0.6)
Insurance plan/payer type, n (%)					
Commercial only	53,151 (64.9)	13,191 (77.1)	5,423 (67.4)	4 (0.0)	0 (0.0)
Commercial and Medicare	4,904 (6.0)	427 (2.5)	1,938 (24.1)	2,004 (10.4)	0 (0.0)
Medicare only	17,246 (21.1)	57 (0.3)	128 (1.6)	17,028 (88.5)	5,010 (99.5)
Medicaid only	6,560 (8.0)	3,439 (20.1)	560 (7.0)	204 (1.1)	23 (0.5)
Index RSV diagnosis code, n (%)					
Pneumonia due to RSV	12,842 (15.7)	2,126 (12.4)	1,121 (13.9)	7,493 (38.9)	2,956 (58.7)
Acute bronchitis or acute bronchiolitis due to RSV	58,718 (71.7)	12,099 (70.7)	5,761 (71.6)	9,553 (49.7)	1,458 (29.0)
RSV or RSV as the cause of disease classified elsewhere	10,301 (12.6)	2,889 (16.9)	1,167 (14.5)	2,194 (11.4)	619 (12.3)

continued on next page

TABLE 1 Baseline Characteristics During the 6-Month Period Prior to the Index Date (continued)

	Aged ≥18 years	Aged 18-59 years at high risk of severe RSV ^a	Aged 60-64 years	Aged ≥65 years	Aged ≥85 years
RSV recorded during hospitalization, n (%)	10,283 (12.6)	3,151 (18.4)	1,396 (17.3)	4,221 (21.9)	1,343 (26.7)
Quan-CCI, mean ± SD (median)	1.1 ± 1.9 (0.0)	1.4 ± 1.9 (1.0)	1.4 ± 2.1 (1.0)	2.3 ± 2.5 (2.0)	2.6 ± 2.3 (2.0)
Baseline respiratory-related conditions, n (%)					
Acute upper respiratory illness (eg, nasopharyngitis, sinusitis)	22,487 (27.5)	6,364 (37.2)	2,188 (27.2)	4,310 (22.4)	1,041 (20.7)
Chronic obstructive pulmonary disease	9,887 (12.1)	3,234 (18.9)	1,299 (16.1)	5,354 (27.8)	1,425 (28.3)
Pneumonia (nonviral)	10,471 (12.8)	2,372 (13.9)	1,006 (12.5)	5,958 (31.0)	2,225 (44.2)
Asthma	8,190 (10.0)	5,380 (31.4)	919 (11.4)	1,891 (9.8)	389 (7.7)
Bronchitis or bronchiolitis	8,788 (10.7)	2,780 (16.2)	991 (12.3)	2,319 (12.1)	575 (11.4)
Baseline cardiovascular-related conditions, n (%)					
Hypertension	26,100 (31.9)	6,134 (35.8)	3,697 (45.9)	10,881 (56.6)	3,214 (63.9)
Coronary artery disease	8,781 (10.7)	2,137 (12.5)	1,108 (13.8)	5,536 (28.8)	1,615 (32.1)
Congestive heart failure	7,120 (8.7)	1,533 (9.0)	710 (8.8)	4,778 (24.8)	1,869 (37.1)
Baseline immune system disorders, n (%)					
Impaired immune system	1,323 (1.6)	850 (5.0)	249 (3.1)	224 (1.2)	22 (0.4)
HIV	395 (0.5)	343 (2.0)	30 (0.4)	13 (0.1)	1 (0.0)
Baseline diabetes, n (%)	12,741 (15.6)	3,221 (18.8)	1,969 (24.5)	5,108 (26.5)	1,115 (22.2)

^aPatients at high risk of severe RSV were defined as those with at least 1 diagnosis for 1 of the following conditions prior to the index date: asthma, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, HIV/AIDS, or impaired immune system.

^bIn Optum, dates of birth are set to a minimum of 1930; therefore, the exact age could not be calculated for all patients and the mean age could not be reported. In addition, patients aged 85 years or older could not be identified prior to 2016.

Quan-CCI = Quan-Charlson Comorbidity Index; RSV = respiratory syncytial virus.

respectively. In addition, similar weekly cost results were observed in Optum and MarketScan when removing the COVID-19 period from the analysis ([Supplementary Figure 2](#)).

Discussion

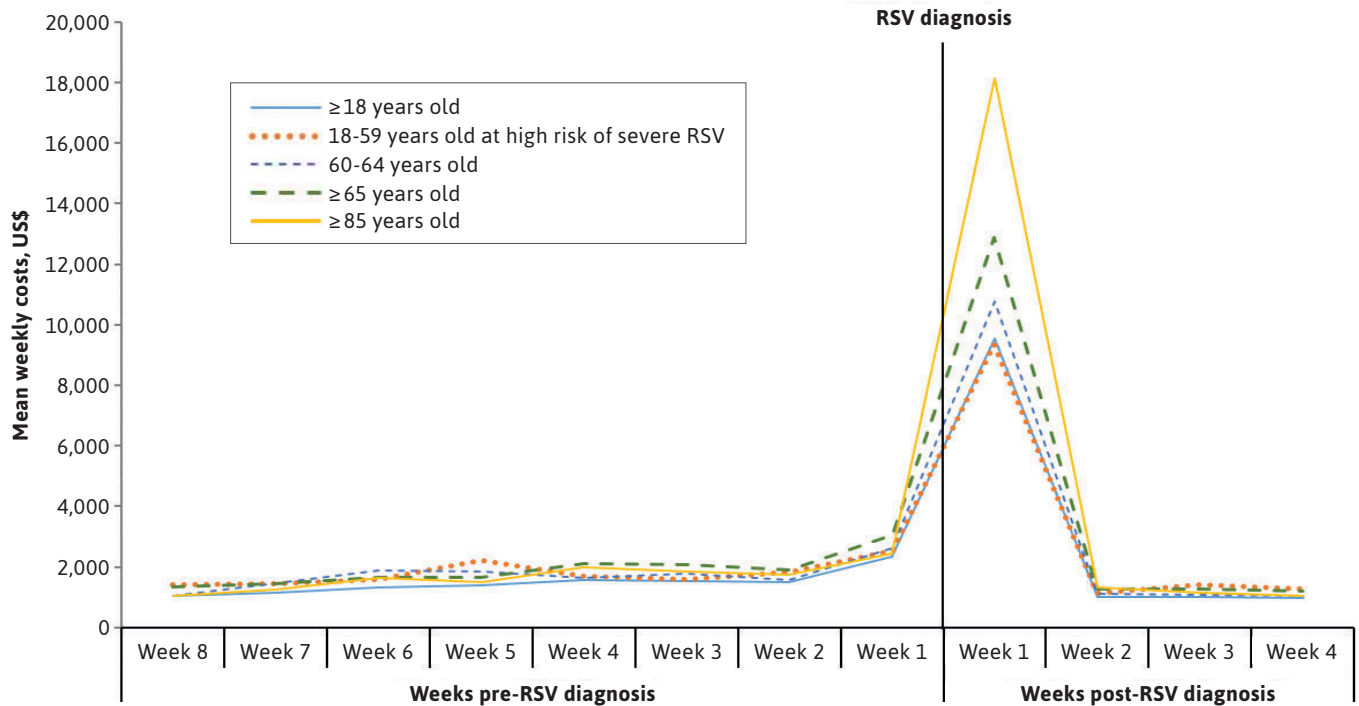
This retrospective analysis based on 2 large claims databases found that among adult patients, annual ICD-coded incidence rates of RSV per 100,000 population ranged from 22.0 to 52.9 in Optum and from 23.4 to 63.6 in MarketScan. Incidence rates were higher among patients aged 60-64 years, 65 years or older, 85 years or older, and 18-59 years at high risk of severe RSV. RSV infection peaked during winter, with seasonal trends more pronounced among patients aged 65 years or older and 85 years or older. The overall RSV incidence also appeared higher in recent years, which may be due to the availability of more rapid and accurate diagnostics that lead to the identification of more positive cases and detection of longer RSV seasons. This was corroborated

by CDC data, which showed the more prominent role of PCR tests in RSV detection in recent years.^{22,23} However, data for the last season available (ie, July 2019 to June 2020) should be interpreted with caution, since this season overlapped with the onset of the COVID-19 pandemic in the United States (March 2020). This overlap in timing may have resulted in a decrease in RSV incidence after the pandemic started because of quarantine rules and increased awareness regarding protection against respiratory infections.

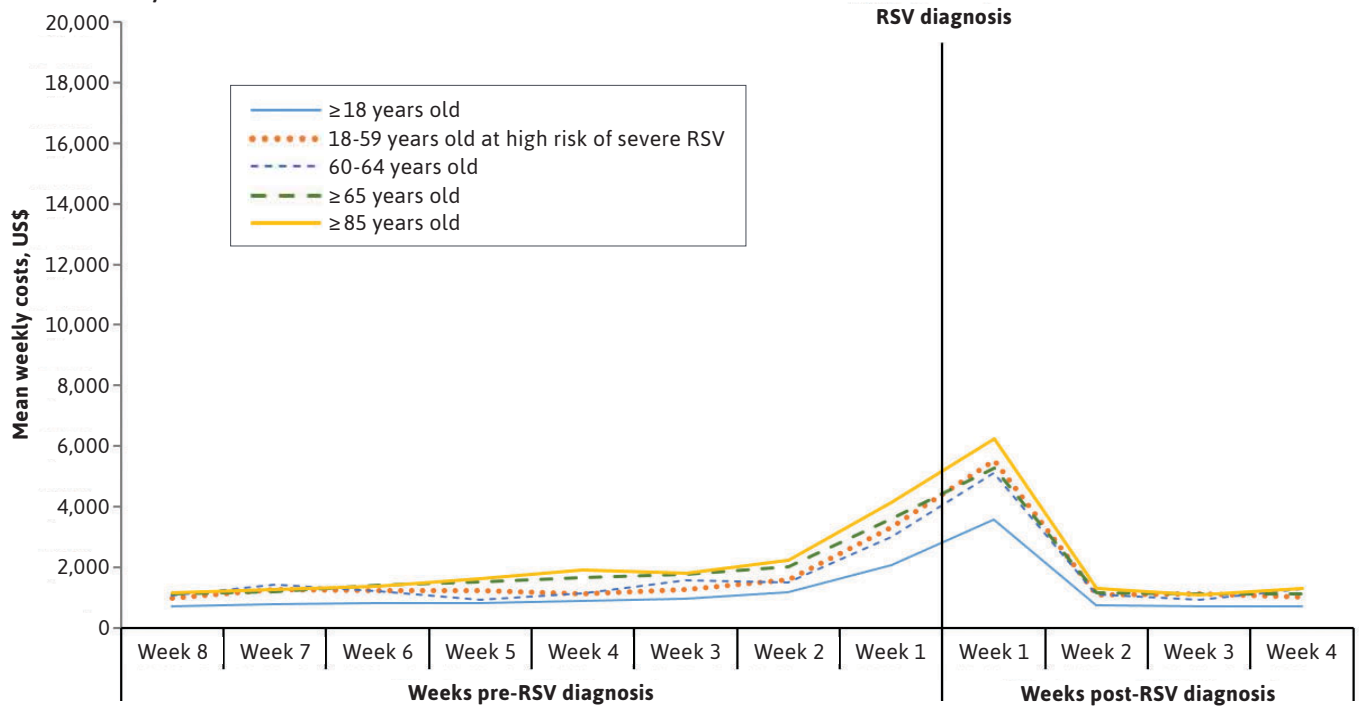
A recent retrospective US claims-based study conducted by Tong et al¹⁹ found higher incidence of RSV compared with findings from this study. The annual RSV incidence rates per 100,000 population were reported to reach 330 among patients aged 65-74 years, 550 among patients aged 75-84 years, and 810 among patients aged 85 years or older. Of note, the measure of RSV incidence in the Tong et al study was based on diagnoses for both RSV-specific and RSV-attributable respiratory conditions, such as pneumonia, acute bronchiolitis, and obstructive chronic

FIGURE 2 All-Cause Weekly Health Care Costs

A. All-cause weekly health care costs for the Optum database



B. All-cause weekly health care costs for the MarketScan database



RSV=respiratory syncytial virus.

bronchitis. Specifically, the authors assumed 9% of the abovementioned respiratory conditions were attributable to RSV based on a previous report,²⁴ which estimated the percentage of pneumonia caused by RSV by using the rates of RSV-associated pneumonia hospitalizations among older adults from several studies. Although the suitability of extrapolating pneumonia data of older adults to other RSV-related respiratory conditions in all populations is open for discussion, this broadened definition of RSV incidence likely explains the higher incidence rates compared with the current study, which was strictly based on ICD-coded RSV. Nonetheless, estimates in the current study are lower than those found in prospective studies,^{6,18,20,21} and this also points to the possibility that without accounting for undiagnosed RSV patients with RSV-attributable respiratory conditions, the burden of RSV is likely underestimated.

In addition to the evaluation of RSV incidence rates, the current study revealed increases in costs in the week before and after RSV diagnosis in all populations. The largest increases in mean weekly costs in both databases were generally observed among patients aged 65 years or older, 85 years or older, and 18–59 years at high risk of severe RSV. Most existing studies on the economic burden of RSV have focused on infants and young children^{13–16} and few analyzed health care costs across age groups. The retrospective case-control study conducted by Amand et al¹⁷ compared total annual health care costs between patients with RSV and matched controls and found incremental costs of \$2,825, \$12,030, and \$16,752 (2014 US dollars) in patients with RSV aged 18–49 years, 65–74 years, and 85 years or older, respectively. Although the dollar amounts cannot be directly compared to those in the current study because of differences in methodologies, both studies similarly identified a general trend of increased costs incurred by patients with more advanced age, demonstrating the substantial burden of RSV among older adult patients. Additionally, the current study assessed weekly costs at different timepoints prediagnosis and postdiagnosis and revealed cost increases in the week leading to RSV diagnosis. This may be attributable to a delay between symptom appearance, diagnostic testing being performed, and availability of testing results that confirm a diagnosis.²⁵ In other words, a patient may start receiving care for symptom management and testing the week before having a record with an ICD code for RSV, which contributes to the increased costs prediagnosis. Another notable observation for all age groups is the lower costs at weeks 2–4 post-RSV compared with the costs at weeks 2–8 pre-RSV. A possible explanation may be “medical fatigue,” in which patients may prefer to stay home after their medical visits for RSV. Patients may also have taken the opportunity to settle other health issues during these

visits, which may lead to reduced costs associated with pharmacy and medical care in weeks 2–4 post-RSV.

The current findings on RSV incidence represent an underestimation, as the analyses focused on medically attended patients who had a claim with an ICD code for RSV. It is known that the clinical presentations of RSV infections are highly similar to those caused by influenza or other respiratory viruses.²⁶ Additionally, it has been shown that RSV is not always considered in the differential diagnosis and, hence, is often not specifically tested for in adults presenting with flu-like symptoms.¹⁰ These factors may contribute to misdiagnosis/underdiagnosis of RSV. Meanwhile, patients who experience common cold-/flu-like symptoms may opt to self-manage the illness by purchasing over-the-counter medications. These patients who may have RSV but do not seek medical services were not captured by the current claims analysis. A prospective follow-up study in older adult patients found that 31% of patients diagnosed with RSV infection visited the physician's office when they experienced symptoms.^{6,27} The same study found the annual incidence of RSV infections (validated via viral culture, RT-PCR, and serology) among older adults and high-risk adults to be 5.5%, among which about one-tenth of patients were asymptomatic.⁶ Another prospective study among hospitalized adults with RSV in 3 US medical centers showed that the annual incidence of RSV was 44.2–58.9 per 100,000 population among the study cohort and 136.9–225.6 per 100,000 population among patients aged 65 years or older.¹⁸ Two other prospective community cohort studies found that RSV incidence was 1,540 and 1,390 per 100,000 population among adults aged 50 years or older and 60 years or older, respectively.^{20,21} The RSV incidence rates identified in these prospective studies are higher than those in the current analysis likely because of active surveillance and the focus on high-risk patients; together, these findings indicate that the issue of underdiagnosed RSV infection can be profound in the real world. It is important to recognize that misdiagnosis/underdiagnosis of RSV infection can be costly given additional resources spent on testing and other care services. Delays in diagnosis may also exacerbate RSV symptoms and lead to suboptimal clinical outcomes. Therefore, additional efforts are needed to identify misdiagnosed/undiagnosed patients with RSV and quantify their burden to fully capture the total economic burden of the disease.

The high incidence and substantial burden of RSV infection among adults identified in this study highlights the need to raise awareness on the consequences of RSV in this population, particularly among older adults and high-risk individuals. In addition to the development and implementation of more rapid and inexpensive

diagnostic testing and RSV-specific treatments,⁹ patients may also benefit from prophylactic options, such as vaccination. Vaccination may not only reduce the incidence of infections but also mitigate the prevalence of severe symptoms, hospitalizations, and death for those who eventually become infected, as evidenced by the recent COVID-19 vaccines.²⁸⁻³⁰ Consequently, RSV vaccination would be particularly beneficial for vulnerable individuals who are at a higher risk of developing severe symptoms associated with RSV, such as those with advanced age and comorbidities.²⁶ Currently, the only approved prophylactic RSV therapy in the United States is a neutralizing monoclonal antibody indicated for high-risk infants,³¹ and no vaccine for active immunization is available.^{32,33} Nonetheless, several RSV vaccine candidates are under active investigations and several candidates developed for infant/maternal/older adult immunization have moved past preclinical and phase 1 trials.^{34,35} Specifically, 2 of the investigational vaccines (1 for infants and 1 for older adults) have received breakthrough therapy designations by the US Food and Drug Administration based on substantial improvements in clinically significant endpoints.³⁶⁻³⁸ With potential new vaccines on the horizon, accompanying policies would need to be considered to optimize vaccine uptake, particularly among those at increased risk of serious outcomes, which may include respiratory failure and death.^{5,9} In this regard, the stratified data in the current analysis that delineated the populations most vulnerable to RSV infections may add value to the development of optimal vaccination policy.

LIMITATIONS

In addition to the inability to identify misdiagnosed/undiagnosed patients, study findings should be considered in light of other limitations. Although

the study used 2 large claims databases covering multiple payer types, claims data relied on RSV diagnosis codes collected for reimbursement purposes and additional information needed to assess RSV diagnosis, such as diagnostic testing results, were not available. Therefore, it was not possible to determine how the RSV diagnosis was established (eg, whether it was validated by laboratory testing). By focusing on ICD-coded RSV, the current analyses may have captured more severe, medically attended RSV cases and overestimated per-patient costs. Meanwhile, payment amounts for patients with capitated plans may have been underestimated because of limited financial information in encounter records. Furthermore, the analysis of weekly costs included patients with unequal follow-up times post-index to avoid survival bias associated with requiring a minimum follow-up. To minimize this limitation, weekly costs post-index were calculated only among patients with available follow-up during the corresponding week. The results may not be generalizable to the entire US population, given that analyses were restricted to health-insured patients. For example, it has been suggested that poverty is associated with an increased rate of RSV hospitalizations;³⁹ thus, the lack of data from uninsured individuals, which likely comprise a higher proportion of low-income individuals, may have led to an underestimation of RSV incidence. Furthermore, claims databases may contain billing errors or omissions in coded claims. Finally, no P values were generated and no adjustments were made for baseline confounders.

Conclusions

This real-world study found that the incidence of medically attended, ICD-coded RSV in adults was 22.0–63.6

per 100,000 population, a likely underestimation since RSV was not systematically tested and only RSV-coded cases were observed. Among patients with ICD-coded RSV, incremental costs associated with RSV were substantial. Incidence rates and costs were higher among patients aged 60 years or older and 18–59 years at high risk of severe RSV.

DISCLOSURES

This study was sponsored by Janssen Scientific Affairs, LLC. The sponsor was involved in the study design, interpretation of results, manuscript preparation, and publication decisions.

B. Brookhart and D. Anderson are employees of Janssen Scientific Affairs, LLC, and are stockholders of Johnson & Johnson. C. Rossi, B. Emond, J. Wang, P. Lefebvre, and M.-H. Lafeuille are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to Janssen Scientific Affairs, LLC, which funded the development and conduct of this study and manuscript. M. Mesa-Frias and S. Drummond are former employees of Janssen Scientific Affairs, LLC. L. Lamerato is an employee of Henry Ford Health System and received research funding from Janssen Scientific Affairs, LLC.

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