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MAJOR ARTICLE

Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis

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Background. Adult respiratory syncytial virus (RSV) vaccines are in the late stages of development. A comprehensive synthesis of adult RSV burden is needed to inform public health decision-making.

Methods. We performed a systematic review and meta-analysis of studies describing the incidence of medically attended RSV (MA-RSV) among US adults. We also identified studies reporting nasopharyngeal (NP) or nasal swab reverse transcription polymerase chain reaction (RT-PCR) results with paired serology (4-fold-rise) or sputum (RT-PCR) to calculate RSV detection ratios quantifying improved diagnostic yield after adding a second specimen type (ie, serology or sputum).

Results. We identified 14 studies with 15 unique MA-RSV incidence estimates, all based on NP or nasal swab RT-PCR testing alone. Pooled annual RSV-associated incidence per 100 000 adults ≥65 years of age was 178 (95% CI, 152–204; n = 8 estimates) hospitalizations (4 prospective studies: 189; 4 model-based studies: 157), 133 (95% CI, 0–319; n = 2) emergency department (ED) admissions, and 1519 (95% CI, 1109–1929; n = 3) outpatient visits. Based on 6 studies, RSV detection was ~1.5 times higher when adding paired serology or sputum. After adjustment for this increased yield, annual RSV-associated rates per 100 000 adults age ≥65 years were 267 hospitalizations (uncertainty interval [UI], 228–306; prospective: 282; model-based: 236), 200 ED admissions (UI, 0–478), and 2278 outpatient visits (UI, 1663–2893). Persons <65 years with chronic medical conditions were 1.2—28 times more likely to be hospitalized for RSV depending on risk condition.

Conclusions. The true burden of RSV has been underestimated and is significant among older adults and individuals with chronic medical conditions. A highly effective adult RSV vaccine would have substantial public health impact.

Keywords. incidence; burden; summary; pooled; underestimated.

Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infection in older adults and adults with chronic medical conditions including cardiopulmonary and immunocompromising conditions [1]. In these patients, RSV can lead to exacerbation of chronic illnesses, hospitalization, and death [1, 2]. Efforts are ongoing to develop RSV prevention strategies, including vaccines for adults [3].

To estimate the potential public health impact that emerging adult RSV prevention strategies might provide, accurate estimates of the burden of RSV in adults are needed. Currently, however, population-based incidence rates of medically attended RSV-associated illness (MA-RSV) in adults, which are the cornerstone of understanding disease burden, have not been systematically reviewed and evaluated. While previous global reviews have attempted to summarize the adult burden of RSV, they have important limitations, including (i) only identifying the proportion of hospitalizations where RSV was identified (rather than incidence), (ii) not including more recently published US estimates, and (iii) not systematically evaluating how RSV burden is influenced by variations in study design and the sensitivity of diagnostic methods [4, 6]. Thus, a comprehensive analysis of population-based rates of adult MA-RSV is needed and can help inform future evaluations of the public health value of RSV prevention strategies.

We performed a systematic literature review and meta-analysis of studies describing population-based rates of MA-RSV among US adults. In addition to summarizing findings across studies, we also examined the impact of, and accounted for, key study characteristics and diagnostic methods on adult RSV rates.

METHODS

Search Strategy and Selection Criteria

We identified published data in PubMed (inclusive of MEDLINE) and Cochrane Library describing MA-RSV rates among adults. Only studies conducted in the United States and published in English were considered. Each article had to

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include at least 1 "RSV term" and "epidemiological measurement term" in the title (Supplementary Table 1). Search results are current through March 1, 2022.

To reduce risk of selection bias, we adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [4]. Two independent reviewers with RSV and epidemiology expertise (F.K. and J.M.M.) screened titles and abstracts identified by the search strategy to create a master list of potentially relevant references for full-text review. Reference lists for studies in this master list were also reviewed. Abstracts for all references flagged for inclusion were reviewed to determine if the report was eligible for analysis. Discrepancies between the 2 independent reviewers were resolved through discussion at each review stage.

We included articles with ≥1 estimated rate of MA-RSV among US adults that reported an RSV case definition (numerator) and a population-based denominator associated with a defined time period. We stratified results by care setting (ie, hospitalized, emergency department [ED], or outpatient) and by age group: 18–49, 50–64, and ≥65 years. Belongia et al. [5] reported RSV rates for adults age ≥60 years only, so we calculated an age-adjusted rate for adults age ≥65 years using age-specific rate ratios for adult pneumonia hospitalization based on a recent population-based study of community-acquired pneumonia (Supplementary Table 2), similar to other meta-analyses [5, 7]. For studies that reported rates for multiple years or for subgroups of our reported age groups, we calculated average age-adjusted rates for our study age groups (Supplementary Table 3). We examined whether studies were prospective or retrospective, how RSV was identified, study period, and whether data were collected from medical records or administrative claims.

Quantifying Nasal/Nasopharyngeal Swab Reverse Transcription Polymerase Chain Reaction Sensitivity

Multiple studies have shown that reverse transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal (NP) or nasal swabs collected upon medical presentation have imperfect sensitivity for detecting RSV [8–12]. We reviewed published literature (including from outside of the United States) to identify studies reporting paired results from NP or nasal swab RT-PCR plus either paired serology specimens (4-fold rise) or sputum (RT-PCR) (Supplementary Table 4). RSV positives from any specimen type were considered true positives. We quantified the relative increase in RSV detection based on adding an additional diagnostic specimen type (ie, adding serology or sputum to NP or nasal RT-PCR alone) by calculating an "RSV detection multiplier" using the following ratio:

$$\frac{RSV\ via\ NP\ or\ nasal\ swab\ +\ RSV\ via\ serology\ or\ sputum}{RSV\ via\ NP\ or\ nasal\ swab\ (alone)}$$

Statistical Analysis

We performed meta-analyses to calculate pooled rates by RSV endpoint and study type using the *metan* command in Stata 14.0. Because in-study and between-study data heterogeneity was anticipated, we used random-effects models [13–15]. Because all estimates included in the meta-analyses were based on RSV detection by RT-PCR of NP or nasal swabs, we applied the median of the RSV detection multiplier (described above) to the pooled meta-analysis results to adjust for underdetection. Specifically, the median value for the RSV detection multipliers identified across studies was applied to the pooled point estimates and lower and upper bounds of the 95% CI to calculate underdetection-adjusted rates and associated uncertainty intervals (UIs). Age-specific US Census population estimates were used to project the expected number of annual US cases from pooled rates.

RESULTS

Search Results

Our search strategy retrieved 3790 articles (Figure 1). After removing duplicates and screening titles and abstracts, 159 required full abstract review. We assessed the full text of 108, of which 14 [15–28] met selection criteria (Table 1). One [28] reported 2 unique MA-RSV rates, resulting in 15 unique estimates.

Study Characteristics

Studies were published between 2007 and 2021, with data collected between 1993 and 2019. Among the 15 estimates, 3 study designs were identified: (i) active prospective surveillance with RSV testing (n = 7/15; 47%) [15, 16, 18, 19, 22, 26, 27], (ii) model-based estimates using the estimated fraction of all cardiopulmonary admissions caused by RSV based on Centers for Disease Control and Prevention (CDC) etiologic surveillance data (n = 4/15; 27%) [17, 23, 28, 29], and (iii) retrospective analyses of administrative claims (ie, RSV identification from pathogen-specific codes only; n = 4/15; 27%) [20, 24, 25, 28]. Nearly all (13/15; 87%) described rates of hospitalization [15–17, 20–28], 4/15 (27%) described ED admission rates [15, 22, 25, 26], and 5/15 (33%) described rates of outpatient visits [15, 18, 19, 22, 25]. Most (12/15; 80%) reported MA-RSV rates for all adults [16–21, 23–26, 28], while 3/15 (20%) reported on subpopulations of older adults (eg, ages ≥50, ≥60, or ≥65 years) [15, 22, 27].

Prospective surveillance studies primarily identified RSV by RT-PCR of NP or nasal swabs collected upon medical presentation (some also included viral culture or throat swabs) [15, 16, 22, 26, 27]. None used serology or sputum. Model-based estimates were derived by applying the proportion of all cardiopulmonary diagnoses thought to be caused by RSV based on seasonal viral surveillance testing conducted by the CDC National Respiratory and Enteric Virus Surveillance System (NREVSS) to overall rates of cardiopulmonary diagnoses.

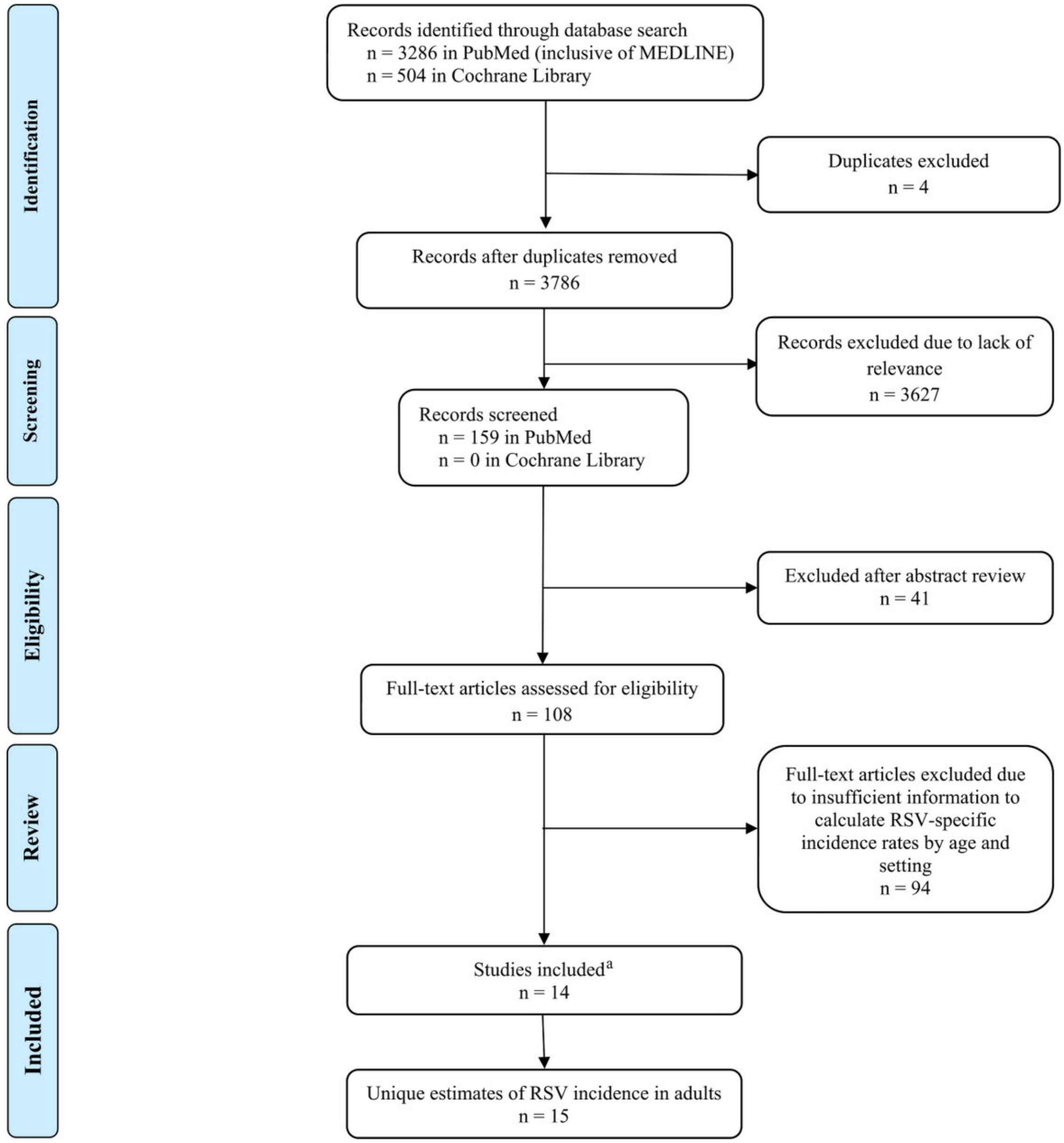

Figure 1. Flow diagram of the literature selection process. [a]Of the 14 studies, 1 study reported >1 RSV incidence of adults based on within-study variations or sensitivity analyses, for a total of 15 unique published incidence estimates in our analysis population. Abbreviation: RSV, respiratory syncytial virus.

Like prospective surveillance studies, NREVSS relies on RT-PCR of NP or nasal swabs to identify RSV [30]. Administrative claims analyses [20, 24, 25, 28] used (only) RSV-coded illness (International Classification of Diseases, Ninth Revision [ICD-9], codes 480.1 [RSV pneumonia], 466.11 [acute bronchiolitis due to RSV], and 079.6 [RSV as the cause of diseases classified elsewhere]).

Associated Hospitalization Rates",5,7,2,0,3mm,3mm,1mm,0mm>Reported RSV-Associated Hospitalization Rates

Reported annual rates of RSV-associated hospitalization per 100 000 from prospective surveillance ranged from 128 to 254 for adults age ≥65 years (n = 5) [15, 16, 22, 26, 27], 51–82 for age 50–64 (n = 4) [16, 22, 26, 27], and 9–21 for age <50 (n = 2) [16, 26]. Among model-based studies, rates ranged from 86–246 for age ≥65 (n = 4) [17, 21, 23, 28], 13–28 for age 50–64 (n = 4) [17, 21, 23, 28], and 1–12 for adults age <50 (n = 4) [17, 21, 23, 28]. Retrospective analysis of administrative claims databases that used only RSV-coded cases for defining hospitalization rates (n = 4) [20, 24, 25, 28] produced results that were much lower, with annual rates <7 per 100 000 persons among all adult age groups (Table 1), suggesting that RSV is inadequately identified using RSV-specific codes alone.

Table 1. Annual Rates of RSV-Associated Hospitalizations, Emergency Department Admissions, and Outpatient Visits per 100 000 US Adults by Estimate Type and Age Group

RSV Burden Estimate by Type	Year of Data	Source of Data	RSV Identification	Annual Rate per 100 000 by Age Group		
				18–49 y	50–64 y	≥65 y
Estimates of RSV-associated hospitalization						
Active, prospective etiologically confirmed						
Branche et al. *Clin Infect Dis* (2021) [16][a]	2017–2020	2 hospitals in Rochester, NY; 5 hospitals in NYC	RT-PCR testing of nasal swab or sputum	9	51	167
Belongia et al. *Open Forum Infect Dis* (2018) [5]	2006–2016	Hospitals and clinics in Marshfield, WI	RT-PCR testing of midturbinate or nasopharyngeal swab			(197)
Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	2009–2010	4 hospitals in Nashville, TN	RT-PCR testing of nasal and throat swabs	21	67	190
McClure et al. *PLoS One* (2014) [22]	2006–2010	Hospitals and clinics in Marshfield, WI	RT-PCR testing of nasopharyngeal swabs	–	78	(128)
Widmer et al. *J Infect Dis* (2012) [27]	2006–2009	4 hospitals in Nashville, TN	RT-PCR testing of nasal and throat swabs	–	82	254
Model-based						
Matias et al. *BMC Public Health* (2017) [21]	1997–2009	HCUP NIS hospital discharge database		9	28	164
Goldstein et al. *Influenza Other Respir Viruses* (2015) [17]	2003–2011	New York hospital database		12	27	89[b]
Zhou et al. *Clin Infect Dis* (2012) [28]	1993–2008	HCUP NIS (13 states) hospital discharge database		1	13	86
Mullooly et al. *Vaccine* (2007) [23]	1996–2000	3 HMOs (Portland, OR; Seattle, WA; Northern CA)		3	23	246[c]
Retrospective claims database (ICD-9 codes)						
Tong et al. *Global Health* (2020) [25]	2008–2014	Truven MarketScan database	ICD-9 codes: 480.1 (RSV pneumonia); 466.11 (acute bronchiolitis due to RSV); and 079.6 (RSV as the cause of diseases classified elsewhere)	<1	1	5
Pastula et al. *Open Forum Infect Dis* (2017) [24]	1997–2012	HCUP NIS hospital discharge database		<1	<1	(6)
Zhou et al. *Clin Infect Dis* (2012) [28]	1993–2008	HCUP NIS (13 states) hospital discharge database		1	1	1
Johnson et al. *J Louisiana State Med Soc* (2012) [20]	1999–2010	Louisiana hospital discharge database		<1	<1	<1
Estimates of RSV-associated emergency department admissions						
Active, prospective etiologically confirmed						
Belongia et al. *Open Forum Infect Dis* (2018) [5]	2006–2016	Hospitals and clinics in Marshfield, WI	RT-PCR testing of midturbinate or nasopharyngeal swab	–	–	(90)
Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	2009–2010	4 hospitals in Nashville, TN	RT-PCR testing of nasal and throat swabs	132	128	340
McClure et al. *PLoS One* (2014) [22]	2006–2010	Hospitals and clinics in Marshfield, WI	RT-PCR testing of nasopharyngeal swabs	–	73	(119)
Retrospective claims database (ICD-9 codes)						
Tong et al. *Global Health* (2020) [25]	2008–2014	Truven MarketScan database	ICD-9 codes: 480.1 (RSV pneumonia); 466.11 (acute bronchiolitis due to RSV); and 079.6 (RSV as the cause of diseases classified elsewhere)	1	1	2
Estimates of RSV-associated outpatient visits						
Active, prospective etiologically confirmed						
Jackson et al. *Clin Infect Dis* (2021) [19]	2018–2019	Kaiser Permanente Washington	RT-PCR testing of nasal and oropharyngeal swab	862	1160	1850
Jackson et al. *J Infect Dis* (2020) [18]	2011–2016	Kaiser Permanente Washington	RT-PCR testing of nasal and oropharyngeal swab	991	1450	2320

Table 1. Continued

RSV Burden Estimate by Type	Year of Data	Source of Data	RSV Identification	Annual Rate per 100 000 by Age Group		
				18–49 y	50–64 y	≥65 y
Belongia et al. *Open Forum Infect Dis* (2018) [5]	2006–2016	Hospitals and clinics in Marshfield, WI	RT-PCR testing of midturbinate or nasopharyngeal swab	–	–	(1391)
McClure et al. *PLoS One* (2014) [22]	2006–2010	Hospitals and clinics in Marshfield, WI	RT-PCR testing of nasopharyngeal swabs	–	1131	(1847)
Retrospective claims database (ICD-9 codes)						
Tong et al. *Global Health* (2020) [25]	2008–2014	Truven MarketScan database	ICD-9 codes: 480.1 (RSV pneumonia); 466.11 (acute bronchiolitis due to RSV); and 079.6 (RSV as the cause of diseases classified elsewhere)	18	28	51

Rates were averaged across seasons when multiple seasons were reported (except Pastula et al.) and are expressed per 100 000 persons per year. Parentheses denote age-adjustment factor applied based on Ramirez et al. [41] (as described in Supplementary Table 2).

Abbreviations: HCUP, Healthcare Cost and Utilization Project; HMOs, Health Maintenance Organizations; ICD-9, International Classification of Diseases, Ninth Revision; NIS, US Nationwide Inpatient Sample; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

[a]Rate calculated based on weighted average of hospital market share from 3 hospital sites.

[b]Weighted average of rates for adults age 65–74 and ≥75 years.

[c]Included only adults who did not receive influenza vaccination.

[d]2012 rate only.

[e]Calculated applying 11.9% hospitalization rate to overall medically attended rate.

[f]Calculated applying 6.1% hospitalization rate to overall medically attended rate.

Associated Rates of ED and Outpatient Visits",5,7,2,0,3mm,3mm,1mm,0mm>Reported RSV-Associated Rates of ED and Outpatient Visits

Estimates for annual ED admission rates (without hospitalization) from prospective surveillance ranged from 90 to 340 per 100 000 adults age ≥65 years (n = 3) [15, 22, 26] and 73 to 128 for adults age 50–64 (n = 2) [22, 26]. Only 1 prospective study estimated ED rates (132 per 100 000) in adults age <50 (Table 1) [26]. Annual rates of RSV-associated outpatient visits from prospective surveillance ranged from 1391 to 2320 per 100 000 adults age ≥65 (n = 4) [15, 18, 19, 22] and 1131 to 1450 for adults age 50–64 (n = 3) [18, 19, 22]. Two prospective surveillance studies reported rates of outpatient visits for RSV (862 and 991 per 100 000) in adults age <50 (Table 1) [18, 19]. One retrospective database study [25] reported rates of ED and outpatient disease that were much lower than other studies.

Impact of Underlying Chronic Medical Conditions

Three papers evaluated risk factors for RSV [15, 16, 21]. One [21] compared RSV hospitalization rates among high-risk patients (ie, history of chronic obstructive pulmonary disease, stroke, diabetes, immunosuppression, or central nervous system, kidney, or liver disorders) with those of adults without these conditions. Depending on age group, high-risk adults had 3–10 times higher RSV hospitalization rates. Another study [15] reported that adults with chronic cardiopulmonary disease were roughly twice as likely to have a medically attended RSV-associated visit compared with those without. Branche et al. [16] found that RSV-associated hospitalization ranged from 1.2 times higher for the obese to 28 times higher for those with congestive heart failure (Table 2).

Impact of Adding Serology or Sputum Specimens

Four studies reported NP swab RT-PCR plus testing of paired serology specimens [8, 11, 12, 31]. Three reported NP or nasal swab RT-PCR plus sputum (Table 3) [9, 10, 31]. Adding paired serology specimens (4-fold rise considered positive) to NP or nasal swabs increased RSV detection by 34%–64% over NP swab RT-PCR alone (*RSV detection multiplier*: 1.4–1.6). Two estimates were based on acute and convalescent specimens (38% and 50%) [12, 31], 1 was pre- vs postseason (64%) [11], and 1 was a combination of these (34%) [8]. Sputum RT-PCR increased RSV detection by 39% to 100% over NP or nasal swab RT-PCR alone (*RSV detection multiplier*: 1.4–2.0) [9, 10, 31]. The median RSV detection multiplier was 1.5x. This value was applied to incidence estimates identified in our review to generate revised incidence estimates that were adjusted for underdetection of RSV based on the relative increase of adding serology or sputum to NP or nasal RT-PCR alone (Table 3; Supplementary Table 5).

analysis",5,7,2,0,3mm,3mm,1mm,0mm>Meta-analysis

Because RSV rates from administrative claims databases were much lower than other study types (suggesting that adult RSV is not adequately detected in these studies), only prospective surveillance or modeling estimates were included in pooled analyses. Estimates from McClure et al. [22] were also excluded from the pooled hospitalization rate for adults age ≥65 years because Belongia et al. [5] reported an updated estimate including all data from McClure et al. Thus, 8/14 reported rates of RSV-associated hospitalization were included in the meta-analysis.

Pooled reported annual rates of RSV-associated hospitalization per 100 000 among adults were 178 (95% CI, 152–204;

Table 2. Rates of Medically Attended RSV-Associated Illness per 100 000 US Adults by Chronic Conditions by Age Group

Study	Outcome	Chronic Condition	Age Group	Rate per 100 000 With Condition	Rate per 100 000 Without Condition	IRR
Branche et al. *Clin Infect Dis* (2021) [16][a]	Hospitalizations	COPD	18–49	32	8	4.0
			50–64	207	33	6.3
			≥65	900	103	8.7
		Asthma	18–49	15	7	2.3
			50–64	97	36	2.7
			≥65	297	123	2.4
		Diabetes	18–49	71	6	11.3
			50–64	116	34	3.4
			≥65	444	97	4.6
		Obesity	18–49	9	7	1.3
			50–64	49	40	1.2
			≥65	158	127	1.2
		CAD	18–49	37	8	4.7
			50–64	159	40	3.9
			≥65	529	102	5.2
		CHF	20–39	237	9	27.6
			40–59	403	23	17.5
			60–79	630	89	7.1
			≥80	1131	254	4.5
Belongia et al. *Open Forum Infect Dis* (2018) [5]	Medically attended	Cardiopulmonary	≥60	196	103	1.9
Matias et al. *BMC Public Health* (2017) [21]	Hospitalizations	High (COPD, diabetes, immunosuppression, stroke, or disorders of cardiovascular system, CNS, kidney, or liver)	18–49	8	3	2.7
			50–64	52	5	9.8
			≥65	242	42	5.7

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; IRR, incidence rate ratio; RSV, respiratory syncytial virus.

[a]Rates for study hospitals in Rochester, NY, and New York City, NY, were pooled based on reported market share and Census population.

n = 8) for age ≥65 years, 45 (95% CI, 27-62; n = 8) for age 50-64, and 8 (95% CI, 6-11; n = 6) for age <50. For the 4 prospective studies, pooled rates were 188 (95% CI, 167–208) for age ≥65, 66 (95% CI, 49–84) for age 50-64, and 13 (95% CI, 2–23) for age <50. These same estimates for the 4 model-based studies were 157 (95% CI, 96–218) for age ≥65, 27 (95% CI, 21–34) for age 50-64, and 7 (95% CI, 4–11) for age <50. After adjusting for underdetection of RSV by NP or nasal swab RT-PCR alone (ie, after applying the RSV detection multiplier of 1.5x), overall pooled estimates of annual RSV-associated hospitalization rates per 100 000 were 267 (UI, 228-306) for age ≥65, 67 (UI, 40-94) for age 50-64, and 13 (UI, 8-17) for age <50 (Table 4). For prospective studies, adjusted pooled rates were 282 (UI, 251–313) for age ≥65, 100 (UI, 73–125) for age 50-64, and 19 (UI, 3–35) for age <50. These same estimates for the 4 model-based studies were 236 (UI, 144–327) for age ≥65, 41 (UI, 31–51) for age 50-64, and 11 (UI, 5–17) for age <50.

Pooled reported annual ED admission rates per 100 000 were 133 (95% CI, 0–319; n = 2) for age ≥65 years, 74 (95% CI, 59–88; n = 2) for age 50-64, and 132 (95% CI, 67–253; n = 1) for age <50. After adjustment for underdetection, ED rates were 200 (UI, 0–478) for age ≥65, 110 (UI, 89-132) for age 50-64, and 198 (UI, 101–380) for age <50. Pooled reported rates of outpatient visits per 100 000 were 1519 (95% CI, 1109–1929; n = 3) for age ≥65, 1148 (95% CI, 935–1361; n = 3) for age 50-64, and 934 (95% CI, 381–1488; n = 2) for age <50. After adjustment for underdetection, these same estimates were 2278 (UI, 1663-2893) for age ≥65, 1722 (UI, 1403-2041) for age 50-64, and 1401 (UI, 571-2231) for age <50 (Table 4). Using these rates, we estimated the number of hospitalizations, ED admissions, and outpatient visits occurring each year in the United States (Supplementary Table 6).

DISCUSSION

Our meta-analysis showed that RSV poses a substantial burden to adults in the United States. Adults ≥65 years of age experience a particularly high RSV burden, with pooled estimates for annual hospitalization of 178 per 100 000 (95% CI, 152-204) based on prospective surveillance and modeling studies (188 for prospective studies; 157 for model-based studies).

Table 3. Increase in RSV Prevalence Associated With Adding Serology or Sputum Specimen Collection to Nasopharyngeal/Nasal Swab for RSV Infection Diagnosis

Study (Year)/ Country	Population	Respiratory Swab and RT-PCR Type	Additional Specimen	Age Group	No. With Both Sample Types	Prevalence With NP/Nasal Swab Alone, %	Prevalence With NP/Nasal Swab and Additional Specimen Type, %	Prevalence Ratio
Falsey (2012) [9] US Rochester	Adults hospitalized with ARI	Nasal (nares/flocked) & throat swabs (2 swabs in same tube) ≤24 h before admission	Sputum	≥18	404	5.7	7.9	1.4
Jeong (2014) [10] Korea	Adults hospitalized with ARI	NP swab (flocked)	Sputum	≥20	154	11.0	18.8	1.7
Falsey (2019) [31] North America/ Europe	Adults age ≥50 y with severe COPD/ CHF enrolled in prospective cohort with medically attended ARI or worsening cardiopulmonary status	Nasal swab within 72 h after qualifying illness	Sputum	≥50	674	2.4	4.7	2.0
			serology: acute and 30 d after illness onset	≥50	1022	2.7	4.1	1.5
Zhang (2016) [12] US CDC	Adult community-acquired pneumonia hospitalizations; n = 936	Combined NP/OP swabs ≤3 d before admission	Serology: admission & convalescent (2–10 wk later)	18–64	623	2.2	2.9	1.3
				≥65	313	3.2	4.8	1.5
				≥18	936	2.6	3.5	1.4
Falsey (2002) [8] US Rochester	Adults with ARI (inpatients & outpatients)	Bilateral NP & OP swabs (3 swabs in same tube) ≤48 h before admission	Serology: baseline or admission & convalescent (4–6 wk later)	≥18	1112	7.8	10.5	1.3
Korsten (2020) [11] Netherlands/ UK/Belgium	Adults ≥60 y enrolled in prospective cohort with ARI (no hospitalizations)	NP swab for incident ARI events (home visit within 72 h)	Serology: preseason and postseason serology within 2 mo of RSV season	≥60	1040	3.5	5.7	1.6

Abbreviations: ARI, acute respiratory infection; NP, nasopharyngeal; OP, oropharyngeal; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

Despite these high rates, our review also revealed that RT-PCR testing of NP or nasal swabs collected upon medical presentation—the methodology upon which all incidence studies we identified were based—has suboptimal sensitivity for detecting RSV [8–12]. Studies that paired results from RT-PCR of NP or nasal swabs with either serology (4-fold-rise) or sputum (RT-PCR) identified a median (range) of 1.5 (1.4–2.0) times as many RSV infections. After adjusting for this underdetection, annual rates of RSV-associated hospitalization were 267 per 100 000 (UI, 228–306; 282 for prospective studies; 236 for model-based studies). Annual rates of ED and outpatient visits in this age group were also high. Applying our (underdetection-) adjusted rates to the 2022 US Census population suggested that roughly 159 000 hospitalizations, 119 000 ED admissions, and 1.4 million outpatient visits occur annually among US adults age ≥65 years because of RSV infection. Assuming a case fatality rate for hospitalized cases of 6%–8% [1, 24], this translates to approximately 9500–12 700 RSV-associated deaths among US adults age ≥65 years each year, which is consistent with prior estimates [29, 32, 33]. Thus, a highly effective vaccine could have tremendous public health impact among older adults, likely comparable to the estimated number of hospitalizations averted from the US seasonal influenza vaccination program in the same age group (13 000–166 000) [34].

Although hospitalization rates were lower among adults age 50–64 and 18–49 years, underdetection-adjusted rates still translated to an estimated 42 000 and 18 000 hospitalizations each year for these age groups, respectively. Most hospitalizations in younger adults occur among those with chronic medical conditions (eg, obesity, diabetes, or chronic cardiopulmonary, kidney, renal, or immunocompromising conditions). These individuals have rates of RSV-associated illness that are 1.2–28 times higher than those without underlying conditions [15, 16, 21].

Although RT-PCR of NP samples is very specific for detecting RSV, the sensitivity of this method may be variable depending on the population and the timing of sample collection during the course of illness. Potential reasons for this include presence of inhibitors in secretions, collection of samples after viral RNA has cleared [35–37], and, in cases of severe disease, virus progression from upper to lower airways before testing [38]. The typical RSV illness begins with a cold and progresses over several days to dyspnea and wheezing. The average time to seek medical attention is 5–6 days; by then, virus may no longer be detectable in the upper airways, and sputum testing may increase diagnostic yield [9, 39]. Not all patients produce sputum samples, however, which can limit diagnostic utility. Serologic analysis is particularly useful for prospective studies where well-timed baseline samples can be paired with acute and convalescent samples. However, rapid amnestic antibody response may obscure a rise in antibody if acute sera collection is delayed, and convalescent samples may not always be available. Overall, the use of sputum in addition to NP swabs enhances diagnostic yield for RSV, and serologic analysis is complementary to PCR for optimally defining true RSV disease burden.

Rates based on RSV-specific ICD codes were roughly 15 times lower than those based on prospective surveillance

Table 4. Pooled Estimates From Random-Effects Model of Rates of RSV-Associated Hospitalizations, Emergency Department Admissions, and Outpatient Visits per 100 000 US Adults by Study Type by Age Group

Summary Estimate by Setting of Care and Age Group	Study	Study Rate (95% CI) per 100 000	Weight %	Pooled Rate (95% CI) per 100 000	Pooled Rate (95% UI) per 100 000 Adjusted for PCR Sensitivity[a]
Hospitalizations					
18–49	*Active surveillance*		*30*	*Active surveillance* 12.5 (1.9–23.2) *Model-based* 7.3 (3.5–11.1) *Overall* 8.4 (5.5–11.2)	*Active surveillance* 18.8 (2.9–34.8) *Model-based* 11.0 (5.3–16.7) *Overall* 12.6 (8.3–16.8)
	Branche et al. *Clin Infect Dis* (2021) [16]	9.1 (5.7–14.5)	27		
	Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	21.1 (10.0–42.0)	3		
	Model-based		*70*		
	Matias et al. *BMC Public Health* (2017) [21]	9.0 (7.0–12.0)	48		
	Zhou et al. *Clin Infect Dis* (2012) [28]	2.1 (1.4–17.2)	11		
	Mullooly et al. *Vaccine* (2007) [23]	3.0 (−7.2 to 14.2)	7		
	Goldstein et al. *Influenza Other Respir Viruses* (2015) [17]	12.1 (−2.1 to 26.1)	4		
50–64	*Active surveillance*		*47*	*Active surveillance* 66.3 (48.9–83.6) *Model-based* 27.1 (20.6–33.7) *Overall* 44.6 (26.7–62.4)	*Active surveillance* 99.5 (73.4–125.4) *Model-based* 40.7 (30.9–50.6) *Overall* 66.9 (40.1–93.6)
	Branche et al. *Clin Infect Dis* (2021) [16]	51.3 (37.5–70.4)	16		
	McClure et al. *PLoS One* (2014) [22]	78.2 (61.0–100.4)	15		
	Widmer et al. *J Infect Dis* (2012) [27]	82.0 (33.0–123.0)	9		
	Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	67.1 (33.0–134.0)	7		
	Model-based		*53*		
	Matias et al. *BMC Public Health* (2017) [21]	28.0 (22.0–36.0)	18		
	Mullooly et al. *Vaccine* (2007) [23]	22.8 (−3.7 to 49.0)	13		
	Zhou et al. *Clin Infect Dis* (2012) [28]	12.8 (2.4–73.9)	11		
	Goldstein et al. *Influenza Other Respir Viruses* (2015) [17]	27.3 (−10.1 to 64.0)	10		
≥65	*Active surveillance*		*61*	*Active surveillance* 187.7 (167.2–208.3) *Model-based* 157.1 (96.1–218.1) *Overall* 177.8 (151.8–203.8)	*Active surveillance* 281.6 (250.8–312.5) *Model-based* 235.7 (144.2–327.2) *Overall* 266.7 (227.7–305.7)
	Belongia et al. *Open Forum Infect Dis* (2018) [5]	197.3 (173.2–227.2)	29		
	Branche et al. *Clin Infect Dis* (2021) [16]	167.1 (136.5–204.8)	24		
	Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	189.6 (104.0–340.0)	4		
	Widmer et al. *J Infect Dis* (2012) [27]	254.0 (131.0–380.0)	4		
	Model-based		*39*		
	Matias et al. *BMC Public Health* (2017) [21]	164.2 (127.1–197.0)	24		
	Mullooly et al. *Vaccine* (2007) [23]	245.9 (154.3–337.6)	7		
	Goldstein et al. *Influenza Other Respir Viruses* (2015) [17]	88.8 (−11.2 to 189.4)	6		
	Zhou et al. *Clin Infect Dis* (2012) [28]	86.1 (37.3–326.2)	3		
Emergency department admissions (all active surveillance)					
18–49	Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	131.8 (67.0–253.0)	100	131.8 (67.0–253.0)	197.7 (100.5–379.5)
50–64	McClure et al. *PLoS One* (2014) [22]	73.1 (59.8–88.9)	99	73.6 (59.1–88.1)	110.4 (88.7–132.2)
	Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	127.6 (44.0–354.0)	1		

Table 4. Continued

Summary Estimate by Setting of Care and Age Group	Study	Study Rate (95% CI) per 100 000	Weight %	Pooled Rate (95% CI) per 100 000	Pooled Rate (95% UI) per 100 000 Adjusted for PCR Sensitivity[a]
≥65	Belongia et al. *Open Forum Infect Dis* (2018) [5]	90.0 (79.0–103.6)	83	133.3 (0–318.6)	200.0 (0–477.9)
	Widmer et al. *Influenza Other Respir Viruses* (2014) [26]	339.6 (117.0–908.0)	17		
Outpatient visits (all active surveillance)					
18–49	Jackson et al. *J Infect Dis* (2020) [18]	990.7 (319.7–1797.9)	56	934.2 (380.8–1487.6)	1401.3 (571.2–2231.3)
	Jackson et al. *Clin Infect Dis* (2021) [19]	862.1 (160.4–1830.0)	44		
50–64	McClure et al. *PLoS One* (2014) [22]	1130.5 (925.0–1374.6)	90	1148.2 (935.4–1360.9)	1722.2 (1403.2–2041.3)
	Jackson et al. *Clin Infect Dis* (2021) [19]	1160.0 (350.0–2170.0)	5		
	Jackson et al. *J Infect Dis* (2020) [18]	1450.0 (550.0–2450.0)	5		
≥65	Belongia et al. *Open Forum Infect Dis* (2018) [5]	1391.4 (1221.2–1601.6)	82	1518.8 (1109.0–1928.7)	2278.2 (1663.4–2893.0)
	Jackson et al. *J Infect Dis* (2020) [18]	2320.0 (1110.0–3680.0)	9		
	Jackson et al. *Clin Infect Dis* (2021) [19]	1850.0 (700.0–3290.0)	9		

Abbreviations: Abbreviations: NP, nasopharyngeal; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; UI, uncertainty interval.

[a]Incidence rate after applying the RSV detection multiplier of 1.5x, which was based on the median relative increase of adding serology or sputum to NP or nasal RT-PCR alone in studies that included multiple RSV detection methods.

or modeling. This likely stems from the infrequency of RSV testing during routine adult care. For example, in a previous study, among 243 RSV infections (29 involving hospitalization) identified by testing previously collected influenza study specimens, only 1 had been diagnosed by standard-of-care testing [18]. Notably, some model-based estimates were >2 times lower than those from prospective surveillance, particularly among older adults [20, 31], suggesting some potential underascertainment in these estimates as well. This could be related to use of only the primary diagnosis code (vs any) to identify cardiopulmonary disease (to which an estimate of RSV positivity was applied). Further, RSV remains an underappreciated pathogen in adults. For example, in a study of 110 adults hospitalized with RT-PCR-documented RSV infection, RSV was listed as the primary discharge diagnosis in only 6% and as a secondary diagnosis in 51% [40].

Our study has limitations. First, our meta-analysis depends on published studies, which have their own potential sources of underestimation including testing only during influenza activity rather than the full RSV season, incomplete or delayed testing of potential RSV infections, and, for modeling studies, reliance on ICD codes to identify cases. Second, few published estimates describe rates of RSV-associated ED or outpatient encounters; however, rates were generally similar across the few studies identified. Similarly, few studies described rates of MA-RSV in younger age groups or identified risk conditions for RSV illness. Finally, although we adjusted our estimates to account for suboptimal sensitivity of RT-PCR of NP or nasal swab samples collected upon medical presentation (based on increased yield of paired serology or sputum) [8–12], even the sensitivity of serology and sputum is imperfect and may miss some RSV cases, particularly serology [8, 12].

Our study adds to the understanding of adult RSV burden by summarizing reported annual rates of MA-RSV for US adults. Importantly, we also adjusted our estimates to account for imperfect sensitivity of NP or nasal swab RT-PCR—the sampling methodology upon which all published rates of MA-RSV have been based to date. By more accurately quantifying the rates of RSV-associated hospitalizations, ED admissions, and outpatient visits, our study provides critical data to inform future public health decision-making about novel adult RSV vaccines, which are on the horizon. More studies are needed to better quantify RSV burden outside of the hospital setting, in younger age groups, and for specific risk groups. Finally, future studies of RSV burden should quantify the increased diagnostic yield associated with adding multiple specimen types or serial testing to standard RT-PCR of NP or nasal swabs collected upon medical presentation.

Supplementary Data

Supplementary materials are available at Open Forum 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.

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Patient consent. This study does not include factors necessitating patient consent.

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