2208

Rates of medically-attended RSV among US adults: A systematic review and meta-analysis

John M. McLaughlin, PhD[1], Farid Khan, MPH[1], Elizabeth Begier, MD[1], David L. Swerdlow, MD[1], Luis Jodar, PhD[1], and Ann R. Falsey, MD[2,3]

[1] Pfizer Vaccines, Collegeville, PA, USA

[2] Department of Medicine, Division of Infectious Diseases, University of Rochester, Rochester, NY, USA

[3] Rochester General Hospital, Rochester, NY, USA

Corresponding Author:
Elizabeth Begier, MD
Elizabeth.Begier@pfizer.com

Alternate Corresponding Author:
Farid Khan, MPH
farid.khan2@pfizer.com

Abstract

Background
Adult respiratory syncytial virus (RSV) vaccines are in 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 RT-PCR results with paired serology (four-fold-rise) or sputum (RT-PCR) to calculate RSV detection ratios quantifying improved diagnostic yield after adding a second specimen type (i.e., 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 ≥65 years were 267 hospitalizations (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.

Background

- Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infection in older adults and adults with particular chronic medical 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]
- Previous global reviews on the adult burden of RSV had limitations[4, 5]

Objective

We performed a systematic literature review and meta-analysis of studies describing population-based rates of MA-RSV among US adults and examined the impact of, and accounted for, key study characteristics and diagnostic methods on adult RSV rates

Methods

Search Strategy
- Identified all publications (in English) describing MA-RSV rates among adults available in PubMed (inclusive of MEDLINE) and the Cochrane Library as of March 1, 2022
- Included all articles with a clear case (numerator) definition of RSV and have a population-based denominator for a defined time period

Study Characteristics Evaluated
- Care settings: OP, ED (not resulting in inpatient admission), and IP
- Age groups (years): 18–49; 50–64; ≥65
- Examined whether studies were prospective or retrospective, how RSV was identified, and whether data were collected from medical records or administrative claims
- In certain instances[7], MA-RSV rates had to be calculated from the published rates

Quantifying Nasal/Nasopharyngeal Swab RT-PCR Sensitivity
- Reviewed published literature (including from outside of the US) reporting paired results from NP or nasal swab RT-PCR plus either paired serology specimens (four-fold rise) or sputum (RT-PCR)
- RSV positives from any specimen type were considered true positives.
- Calculated the relative increase in RSV detection based on added specimen type:

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

Statistical Analysis
- Meta-analyses to calculate pooled rates by RSV endpoint and study type using random effects modeling in Stata 14.0 (StataCorp LLC, College Station, Texas)
- The median value for the RSV detection multipliers (described above) identified across studies was applied to the pooled point estimates and lower and upper bounds of the 95% confidence interval (CI) to calculate under detection-adjusted rates and associated uncertainty intervals (UI)
- Age-specific US Census population estimates were used to project the expected number of annual US cases from pooled rates

Results

- 14 studies met selection criteria, with 1 reporting 2 unique estimates for a total of 15 estimates **(Figure 1)**
- ***Full tables are published online via QR code***
- Annual rates of RSV-associated hospitalization are shown in **Table 1**
- Annual ED admission rates from prospective surveillance ranged from 90–340 per 100,000 adults ≥65 years (n=3)[8, 12, 13] and 73–128 for 50–64 (n=2)[12, 13]
- Only one prospective study estimated ED rates (132 per 100,000) in adults <50[13]
- Annual rates of RSV-associated outpatient visits from prospective surveillance ranged from 1391–2320 per 100,000 adults ≥65 (n=4)[8, 10-12] and 1131–1450 for 50–64 (n=3)[10-12]
- 3 studies evaluated risk factors for MA-RSV (**Table 2**)
- 4 studies reported NP swab RT-PCR plus testing of paired serology specimens[23-26] and three paired with sputum[24, 27, 28] (**Table 3**)
- After applying the RSV detection multiplier of 1.5x, overall pooled estimates of annual RSV-associated hospitalization rates were 267 (UI:228–306) for ≥65, 67 (40–94) for 50–64, and 13 (8–17) for <50 (**Table 4**)
- Applying our (under-detection) adjusted rates to the 2022 US Census population suggests that roughly 159,000 hospitalizations, 119,000 ED admissions, and 1.4 million outpatient visits occur annually among US adults ≥65 years because of RSV infection (**Table 5**)

Results (continued)

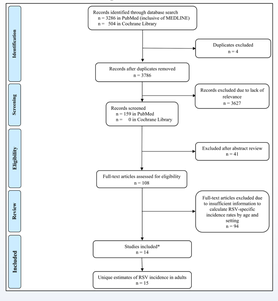
Table 1. Annual Rates of RSV-Associated Hospitalization per 100,000 US Adults by Estimate Type and Age Group

Study	Year of data	Source of data (RSV identification)	Rate per 100,000 by age group		
			18–49 y	50–64 y	≥65 y
Active, prospective etiologically confirmed					
Branche et al. CID (2021)[9]	2017 – 2020	7 hospitals in NY (RT-PCR, nasal swab or sputum)	9	51	167
Belongia et al. OFID (2018)[8]	2006 – 2016	Hospitals/clinics in Marshfield, WI (RT-PCR, midturbinate or NP swabs)			(197)
Widmer et al. Infl Oth Resp Vir (2014)[13]	2009 – 2010	4 hospitals in Nashville, TN (RT-PCR, nasal and throat swabs)	21	67	190
McClure et al. PLoS One (2014)[12]	2006 – 2010	Hospitals/clinics in Marshfield, WI (RT-PCR, NP swabs)	–	78	(128)
Widmer et al. JID (2012)[14]	2006 – 2009	4 hospitals in Nashville, TN (RT-PCR, nasal and throat swabs)	–	82	254
Model-based					
Matias et al. BMC Pub Hlth (2017)[22]	1997 – 2009	HCUP NIS hospital discharge database	9	28	164
Goldstein et al. Infl Oth Resp Vir (2015)[15]	2003 – 2011	NY hospital database	12	27	89[b]
Zhou et al. CID (2012)[16]	1993 – 2008	HCUP NIS (13 states) hospital discharge database	1	13	86
Mullooly et al. Vaccine (2007)[21]	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)[18]	2008 – 2014	Truven MarketScan© database	<1	1	5
Pastula et al. OFID (2017)[15]	1997 – 2012	HCUP NIS hospital discharge database	<1	<1	(6)
Zhou et al. CID (2012)[16]	1993 – 2008	HCUP NIS (13 states) hospital discharge database	1	1	1
Johnson et al. J LA State Med Soc (2012)[17]	1999 – 2010	Louisiana hospital discharge database	<1	<1	<1

HCUP = Healthcare Cost and Utilization Project; NIS = US Nationwide Inpatient Sample; HMOs = Health Maintenance Organizations. Rates averaged across seasons when multiple seasons were reported (except Pastula et al.) and are expressed as per 100,000 persons per year. Parentheses denote age-adjustment factor applied based on Ramirez et al[7]

a. Rate calculated based on weighted average of hospital market share from three hospital sites.
b. Weighted average of rated for adults aged 65–74 and ≥75 years.
c. Included only adults who did not receive influenza vaccination.

Figure 1. Flow Diagram of Literature Selection



* Of the 14 studies, 1 study reported more than one 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.

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

Study	Outcome	Chronic condition	Age group	Rate per 100,000 with condition	Rate per 100,000 without condition	IRR
Branche et al. CID (2021)[9]	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. OFID (2018)[8]	Medically-attended	Cardiopulmonary	≥60	196	103	1.9
Matias et al. BMC Pub Hlth (2017)[22]	Hospitalizations	High Risk*	18-49	8	3	2.7
			50-64	52	5	9.8
			≥65	242	42	5.7

* High Risk = COPD, diabetes, immunosuppressed, stroke, or disorders of cardiovascular, CNS, kidney, or liver

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

Study (Year) Site	Additional Specimen	Age Group	N with Both Sample Types	Prevalence with NP/Nasal Swab Alone	Prevalence with NP/Nasal Swab and Additional Specimen Type	Prevalence Ratio
Falsey (2012)[27] US Rochester	Sputum	≥18	404	5.7%	7.9%	1.4
Jeong (2014)[28] Korea	Sputum	≥20	154	11.0%	18.8%	1.7
Falsey (2019)[24] North America / Europe	Sputum	≥50	674	2.4%	4.7%	2.0
	Serology: Acute and 30 days after illness onset	≥50	1022	2.7%	4.1%	1.5
Zhang (2016)[26] US CDC	Serology: admission & convalescent (2–10 weeks 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)[23] US Rochester	Serology: baseline or admission & convalescent (4–6 weeks later)	≥18	1112	7.8%	10.5%	1.3
Korsten (2020)[25] Netherland / UK / Belgium	Serology: preseason and post season serology within 2 months of RSV season	≥60	1040	3.5%	5.7%	1.6

Figure 2. RSV-Associated Hospitalizations Pooled Estimates Increments by Study Type and Under-ascertainment Adjustment among Adults ≥65 Years

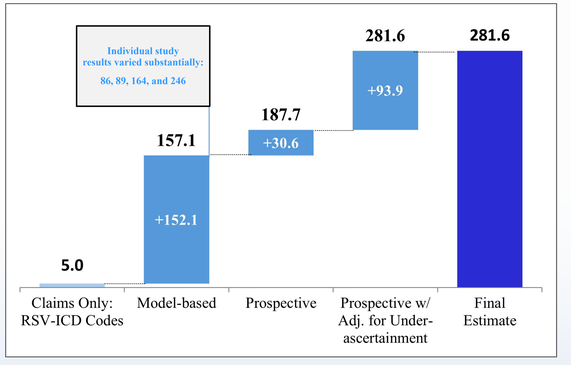


Table 4. Annual Rates of RSV-Associated Hospitalization per 100,000 US Adults by Estimate Type and Age Group

Age Group	Pooled Rate (95%CI) per 100,000	Pooled Rate (95%UI) per 100,000 Adjusted for PCR Sensitivity*
18–49[9,13,22,16,21,19]	Active Surveillance 12.5 (1.9 – 23.2)	Active Surveillance 18.8 (2.9 – 34.8)
	Model-based 7.3 (3.5 – 11.1)	Model-based 11.0 (5.3 – 16.7)
	Overall 8.4 (5.5 – 11.2)	Overall 12.6 (8.3 – 16.8)
50–64[9,12,14,13,22,21,16,19]	Active Surveillance 66.3 (48.9 – 83.6)	Active Surveillance 99.5 (73.4 – 125.4)
	Model-based 27.1 (20.6 – 33.7)	Model-based 40.7 (30.9 – 50.6)
	Overall 44.6 (26.7 – 62.4)	Overall 66.9 (40.1 – 93.6)
≥65[8,9,13,14,22,21,19,16]	Active Surveillance 187.7 (167.2 – 208.3)	Active Surveillance 281.6 (250.8 – 312.5)
	Model-based 157.1 (96.1 – 218.1)	Model-based 235.7 (144.2 – 327.2)
	Overall 177.8 (151.8 – 203.8)	Overall 266.7 (227.7 – 305.7)

* 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.

Table 5. Annual MA-RSV Projections Based on Adjusted Incidence Rates from Study Meta-Analysis

Age Group in Years	Hospitalizations	ED Visits	OP Visits
18–49	17,700	277,731	1,968,507
50–64	42,060	69,409	1,082,785
≥65	159,247	119,391	1,360,322
Total	219,007	466,531	4,411,614

Limitations: Testing only during influenza activity, incomplete or delayed testing of potential RSV infections, and reliance on ICD codes to identify cases. Few published estimates describe rates of RSV-associated ED or outpatient encounters. Few studies described rates of MA-RSV in younger age groups or identified risk conditions for RSV illness. Sensitivity of serology and sputum is imperfect.

Conclusions

- **RSV poses a substantial burden to adults** in the US underscoring the need for novel prevention strategies.
- Applying adjusted rates to the 2022 US Census population suggests that **~159,000 hospitalizations, 119,000 ED admissions, and 1.4 million outpatient visits occur annually among adults ≥65 years** due to RSV infection. An estimated **42,000 adults aged 50–64** and **18,000 aged 18–49** years are **hospitalized each year**. Most hospitalizations in **younger adults** occur among those with **chronic medical conditions**
- **RT-PCR of NP samples** is very specific for detecting RSV; however, **sensitivity may be incomplete in real word setting**. 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
- Our study provides critical data to inform future public health decision-making about **novel adult RSV vaccines**
- **Full publication available online** via OFID open access: https://doi.org/10.1093/ofid/ofac300

References: 1. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. Apr 28 2005;352(17):1749-59. doi:10.1056/NEJMoa043951 2. Respiratory Syncytial Virus (RSV) Infection Trends and Surveillance. Centers for Disease Control and Prevention. https://www.cdc.gov/rsv/research/us-surveillance.html; 3. Bingi C, Dondi A, Scarpini S, et al. Current State and Challenges in Developing Respiratory Syncytial Virus Vaccines. Vaccines. Nov 11 2020;8(4)doi:10.3390/vaccines8040672; 4. Tin Tin Htar M, Yerramalla MS, Moïsi JC, Swerdlow DL. The Burden of Respiratory Syncytial Virus in Adults: A Systematic Review and Meta-Analysis. Epidemiol Infect. Feb 13 2020:1-35. doi:10.1017/S0950268820000400; 5. Shi T, Denouel A, Tietjen AK, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. The Journal of infectious diseases. Oct 7 2020;222(Suppl 7):S577-S583. doi:10.1093/infdis/jiz059; 6. Mohor D, Libersat A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. Jul 21 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097; 7. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Nov 15 2017;65(11):1806-1812. doi:10.1093/cid/cix647; 8. Belongia EA, King JP, Kieke BA, et al. Clinical Features, Severity, and Incidence of RSV Illness During 12 Consecutive Seasons in a Community Cohort of Adults >=65 Years Old. Open Forum Infect Dis. Dec 2018;5(12):ofy316. doi:10.1093/ofid/ofy316; 9. Branche AR, Saiman L, Walsh EE, et al. Incidence of Respiratory Syncytial Virus Infection among Hospitalized Adults, 2017-2020. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Jul 9 2021;doi:10.1093/cid/ciab595; 10. Jackson ML, Scott E, Kuypers J, Nalla AK, Roychoudhury P, Cho HY. Epidemiology of respiratory syncytial virus across five influenza seasons among adults and children one year of age and older - Washington State, 2011/12 - 2015/16. The Journal of infectious diseases. Jun 19 2020;doi:10.1093/infdis/jiaa331; 11. Jackson ML, Starita L, Kinney E, et al. Incidence of Medically Attended Acute Respiratory Illnesses Due to Respiratory Viruses Across the Life Course During the 2018/19 Influenza Season. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. Sep 7 2021;73(5):802-807. doi:10.1093/cid/ciab131; 12. MacCree DL, Kieke BA, Sundaram ME, et al. Seasonal incidence of medically attended respiratory syncytial virus infection in a community cohort of adults >=50 years old. PLoS One. 2014;9(7):e102586. doi:10.1371/journal.pone.0102586; 13. Widmer K, Griffin MR, Zhu Y, Williams JV, Talbot HK. Respiratory syncytial virus- and human metapneumovirus-associated emergency department and hospital burden in adults. Influenza Other Respir Viruses. May 2014;8(3):347-52. doi:10.1111/irv.12254; 14. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. The Journal of infectious diseases. Jul 1 2012;206(1):56-62. doi:10.1093/infdis/jis309; 15. Pastula ST, Hackett J, Coulson J, et al. Hospitalizations for Respiratory Syncytial Virus Among Adults in the United States, 1997-2012. Open Forum Infect Dis. Winter 2017;4(1):ofw278. doi:10.1093/ofid/ofw278; 16. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. May 2012;54(10):1427-36. doi:10.1093/cid/cis211; 17. Johnson JJ, Rateaf R. Respiratory syncytial virus-associated hospitalizations in Louisiana. J La State Med Soc. Sep-Oct 2012;164(5):268-73. ; 18. Tong S, Amand C, Kieffer A, Kyaw MH. Incidence of respiratory syncytial virus related health care utilization in the United States. J Glob Health. Dec 2020;10(2):020242. doi:10.7189/jogh.10.020422; 19. Goldstein E, Greene SK, Olson DR, Hanage WP, Lipsitch M. Estimating the hospitalization burden associated with influenza and respiratory syncytial virus in New York City, 2003-2011. Influenza Other Respir Viruses. Sep 2015;9(5):225-33. doi:10.1111/irv.12325; 20. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or subtype, age, cause of death, and risk status. Influenza Other Respir Viruses. Sep 2014;8(5):507-15. doi:10.1111/irv.12256; 21. Mullooly JP, Bridges CB, Thompson WW, et al. Influenza- and RSV-associated hospitalizations among adults. Vaccine. Jan 15 2007;25(5):846-55. doi:10.1016/j.vaccine.2006.09.041; 22. Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of hospitalization attributable to influenza and RSV in the US during 1997-2009, by age and risk status. BMC Public Health. Mar 21 2017;17(1):271. doi:10.1186/s12889-017-4177-z; 23. Falsey AR, Formica MA, Walsh EE. Diagnosis of respiratory syncytial virus infection: comparison of reverse transcription-PCR to viral culture and serology in adults with respiratory illness. Journal of clinical microbiology. Mar 2002;40(3):817-20. doi:10.1128/jcm.40.3.817-820.2002; 24. Falsey AR, Walsh EE, Esser MT, Shoemaker K, Yu L, Griffin MP. Respiratory syncytial virus-associated illness in adults with advanced chronic obstructive pulmonary disease and/or congestive heart failure. J Med Virol. Jan 2019;91(1):65-71. doi:10.1002/jmv.25285; 25. Korsten K, Adriaenssens N, Coenen S, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. The European respiratory journal. Apr 2021;57(4)doi:10.1183/13993003.02088-2020; 26. Zhang Y, Sakthivel SK, Brumley A, et al. Serology Enhances Molecular Diagnosis of Respiratory Virus Infections Other than Influenza in Children and Adults Hospitalized with Community-Acquired Pneumonia. Journal of clinical microbiology. Jan 2017;55(1):79-89. doi:10.1128/JCM.01701-16; 27. Falsey AR, Formica MA, Walsh EE. Yield of sputum for viral detection by reverse transcription PCR in adults hospitalized with respiratory illness. Journal of clinical microbiology. Jan 2012;50(1):21-4. doi:10.1128/JCM.05841-11; 28. Jeong JH, Kim KH, Jeong SH, Park JW, Lee SM, Seo YH. Comparison of sputum and nasopharyngeal swabs for detection of respiratory viruses. J Med Virol. Dec 2014;86(12):2122-7. doi:10.1002/jmv.23937

Disclosures: This study was funded by Pfizer, Inc.