The Journal of Infectious Diseases

MAJOR ARTICLE

Estimation of the Number of Respiratory Syncytial Virus–Associated Hospitalizations in Adults in the European Union

Richard Osei-Yeboah,[1] Peter Spreeuwenberg,[2] Marco Del Riccio,[2,3] Thea K. Fischer,[4,5] Amanda Marie Egeskov-Cavling,[4,5] Håkon Bøås,[6] Michiel van Boven,[7,8] Xin Wang,[9] Toni Lehtonen,[10] Mathieu Bangert,[11] Harry Campbell,[1] and John Paget,[2] for the Respiratory Syncytial Virus Consortium in Europe (RESCEU) Investigators[a]

[1]Centre for Global Health, Usher Institute, University of Edinburgh, United Kingdom; [2]Netherlands Institute for Health Services Research, Utrecht, The Netherlands; [3]Postgraduate Medical School in Public Health, University of Florence, Italy; [4]Department of Virus and Microbiological Special Diagnostics, Statens Serum Institut, Copenhagen, Denmark; [5]Department of Clinical Research, Nordsjaellands Hospital, Hilleroed and Public Health, University of Copenhagen, Denmark; [6]Department of Infection Control and Vaccines, Norwegian Institute of Public Health, Oslo; [7]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven; [8]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, The Netherlands; [9]School of Public Health, Nanjing Medical University, China; [10]Department of Health Security, Finnish Institute for Health and Welfare, Helsinki; and [11]Sanofi Vaccines, Lyon, France

Background. Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections in adults that can result in hospitalizations. Estimating RSV-associated hospitalization is critical for planning RSV-related healthcare across Europe.

Methods. We gathered RSV-associated hospitalization estimates from the RSV Consortium in Europe (RESCEU) for adults in Denmark, England, Finland, Norway, Netherlands, and Scotland from 2006 to 2017. We extrapolated these estimates to 28 European Union (EU) countries using nearest-neighbor matching, multiple imputations, and 2 sets of 10 indicators.

Results. On average, 158 229 (95% confidence interval [CI], 140 865–175 592) RSV-associated hospitalizations occur annually among adults in the EU (≥18 years); 92% of these hospitalizations occur in adults ≥65 years. Among 75–84 years, the annual average is estimated at 74 519 (95% CI, 69 923–79 115) at a rate of 2.24 (95% CI, 2.10–2.38) per 1000. Among ≥85 years, the annual average is estimated at 37 904 (95% CI, 32 444–43 363) at a rate of 2.99 (95% CI, 2.56–3.42).

Conclusions. Our estimates of RSV-associated hospitalizations in adults are the first analysis integrating available data to provide the disease burden across the EU. Importantly, for a condition considered in the past to be primarily a disease of young children, the average annual hospitalization estimate in adults was lower but of a similar magnitude to the estimate in young children (0–4 years): 158 229 (95% CI, 140 865–175 592) versus 245 244 (95% CI, 224 688–265 799).

Keywords. respiratory syncytial virus; European Union; adults; burden; hospitalization.

Respiratory syncytial virus (RSV) is a major cause of acute respiratory infections (ARIs) in both infants and older adults. In adult populations with RSV infections, lower respiratory tract infection is common and can result in respiratory failure or death [1, 2]. RSV is a common cause of hospitalization for older adults, especially in the winter months, and the commonly associated diagnoses include pneumonia and exacerbations of chronic conditions such as chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and asthma [3–7]. Severe respiratory illnesses resulting from RSV infections with complications that could be compared to those caused by seasonal influenza, often among influenza-immunized populations, have been reported in hospitalized adults [2]. The mean length of hospitalization stay is longer among adults with RSV compared to influenza (6.0 days vs 3.6 days) [8], and an even longer median length of stay of 9 days (Interquartile range: 6–25 days) has been reported in adults hospitalized with RSV [9].

A high burden of RSV hospitalizations among adults, notably older adults and persons with chronic conditions including transplantation, COPD, and CHF, has been reported [10, 11]. Previous studies have reported varying estimates of the incidence of RSV infections in hospitalized adults [5, 11, 12]. Estimating the incidence of RSV infection in hospitalized adults remains challenging as there are no dedicated RSV surveillance systems as well as low levels of routine testing of RSV in patients with an ARI [13], and only more severe cases are

Received 17 February 2023; editorial decision 23 May 2023; accepted 25 May 2023; published online 29 May 2023

[a]The RESCEU investigators are listed in the Acknowledgments.

Correspondence: Richard Osei-Yeboah, PhD, Centre for Global Health, Usher Institute, University of Edinburgh, 30 West Richmond Street, Edinburgh, EH8 9DX, UK (richard.osei-yeboah@ed.ac.uk); John Paget, PhD, Netherlands Institute for Health Services Research, Otterstraat 118, 3513 CR, Utrecht, The Netherlands (j.paget@nivel.nl).

The Journal of Infectious Diseases® 2023;228:1539–48

https://doi.org/10.1093/infdis/jiad189

commonly diagnosed. Other challenges include imperfect reporting of hospitalization *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes [14, 15] and diagnostic testing limitations [16]. A study conducted in 3 European countries across 2 seasons showed that the RSV burden in community-dwelling older adults and adults with comorbidities is substantial and comparable to influenza but rarely caused severe disease [17]. RSV-associated mortality among older adults is reportedly substantial when compared to influenza [18], with the majority of deaths occurring among persons aged ≥60 years [8]. Global estimates indicate that the RSV-associated hospital admission rate and in-hospital case fatality rate are higher among persons aged ≥65 years compared to those aged 50–64 years [12]. Older adults may be more susceptible to viral and bacterial diseases and complications including RSV-associated hospitalizations partly due to immunosenescence [19] and the number of comorbidities that exist in this population [20].

It is recognized that RSV infections are common in older adults in high-income countries [7, 21]. To effectively plan healthcare resource utilization and adequately manage the RSV-related healthcare needs of the older adult population across Europe, including prioritizing preventive care, it is important to understand the RSV disease burden in this population. In this study, we aimed to estimate the numbers and incidence rates of RSV-associated hospital admissions in 28 European Union (EU) countries, including the United Kingdom (UK), and Norway by using data from a previously published RSV Consortium in Europe (RESCEU) study [22] and a literature review.

METHODS

We used a 2-stage approach to estimate RSV-associated hospitalizations in adults across the countries in the EU.

Stage 1: Input Data

In stage 1, we gathered and used modeling inputs from the previously published RESCEU project estimating national RSV-associated average annual hospitalizations and hospitalization rates for adults in Denmark, England, Finland, Norway, the Netherlands, and Scotland from 2006 to 2017 [22]. These studies used time-series regression methods to estimate the RSV-associated numbers and rates of hospitalization.

RSV Hospital Admission Definition in RESCEU Studies

In stage 1, the previous RESCEU studies identified all respiratory hospital admissions using *ICD-10* codes at any point during an admission. The studies extracted all hospital admissions with any mention of respiratory tract infection (RTI), RTI admissions with any mention of pathogen-specific diagnosis code (pathogen-coded admissions), and RTI admissions with an RSV diagnosis code (RSV-coded admissions) [22].

Scoping Literature Review

In addition, to complement RESCEU data, we conducted a scoping literature review in November 2021 to identify estimates that used the same methodology in the RESCEU studies. We searched Medline and Embase electronic databases using predefined terms to identify original articles on RSV-associated hospitalizations (Supplementary File 1). The search broadly focused on national estimates published in European countries between 2000 and 2021. Our search did not apply any language restrictions. Two independent reviewers (R. O.-Y. and M. D. R.) conducted title and abstract screening, full-text screening, and data extraction. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23]. The diagnosis codes used to identify respiratory diagnosis groups of the data sources that provided stage 1 estimates are presented in Table 1.

Stage 2: Statistical Modeling

In stage 2, we extracted the data from the 6 national RESCEU estimates to create the input data. We extrapolated the input data to the EU using 2 different modeling approaches: nearest-neighbor matching, multiple imputations, and 2 sets of 10 indicators (Supplementary File 2) [24]. The indicators were selected based on plausibility [24] and the availability of data in all

Table 1. Diagnosis Codes Used to Identify Respiratory Diagnosis Groups of the Data Sources That Provided Stage 1 Estimates

Author, Year	Country	Period of Observation	Age Groups	Outcome Coding (*ICD-10*)
Johannesen et al, 2022 [22]	Denmark	2010–2017	0–2 mo, 3–5 mo, 6–11 mo, 1–2 y, 3–4 y, 5–17 y,18–64 y, 65–74 y, 75–84 y, ≥85 y	Acute upper respiratory tract infection (J00, J02–J06); pneumonia and influenza (J09–J18); bronchiolitis and bronchitis (J20–J21 J40); unspecified lower respiratory tract infection (J22)
	England	2007–2017		
	Finland	2006–2016		
	Netherlands	2013–2017		
	Norway	2008–2017		
	Scotland	2010–2016		

Abbreviations: ICD-10, International Classification of Diseases, Tenth Revision.

included countries and are not always specific to RSV. The indicators only aim to capture variability across countries. Two sets of indicators were used to reduce bias and ensure that more stable estimates were generated. This resulted in 4 distributions of plausible values for each country. The nearest-neighbor matching approach did not use the physical distance between countries or the geographical locations of countries. It refers to the nearest in terms of rates after comparing/matching as closely as possible countries with data to those with missing data based on the 2 sets of 10 selected indicators. Next, a hierarchical linear model was used to estimate a rate and confidence interval (CI) for each country. These approaches generated 4 sets of estimates, with CIs and the averages of these estimates, and the CIs were reported. We estimated the average number of RSV-associated hospitalizations and the annual hospitalization rates (per 1000 adult population) by age group in the EU (including the UK) and Norway. The outputs of the 2 modeling approaches for the EU are presented in Supplementary Files 3–10.

RESULTS

Scoping Literature Review

Of 1392 citations assessed, 5 were identified to be eligible for inclusion in the analysis. Two of the eligible studies provided estimates only for infants, and data from these studies were not included in this analysis. We found 3 eligible studies providing new estimates for England [25–27], but because there were recent RESCEU estimates for England, the new estimates found from the literature were not included as input data for stage 2. The search records of RSV-associated hospitalization estimates are outlined in a PRISMA flowchart (Figure 1).

Stage 2 Estimates

Number of RSV-Associated Hospital Admissions in 28 EU Countries

Extrapolating the data from 5 EU countries and Norway to 28 EU countries (including the UK), we estimate that on average 158 229 (95% CI, 140 865–175 592) RSV-associated hospitalizations occurred annually among adults aged ≥18 years (Table 2). The highest average annual numbers of RSV-associated hospital admissions among adults aged 18–64 years (2896 [95% CI, 2039–3752]) and ≥85 years (6002 [95% CI, 4028–7976]) were estimated to occur in the UK while the highest average annual RSV-associated number of hospital admissions for adults aged 65–74 years (5387 [95% CI, 3885–6889]) and 75–84 years (13 843 [95% CI, 11 923–15 764]) was estimated to occur in Germany (Table 2). The lowest average annual RSV-associated number of hospital admissions in all age groups occurred in Malta (Table 2). Of the overall RSV-associated hospital admissions, 145 102 (95% CI, 129 961–160 242) occurred among adults aged ≥65 years per year. Among adults aged 75–84 years, we estimate an average annual RSV-associated hospital admission of 74 519 (95% CI, 69 923–79 115) at a rate of 2.24 (95% CI, 2.10–2.38) per 1000 adults per year (Table 3). The highest proportion of RSV-associated hospitalizations (47%) occurred in this age group in the EU as well as in all countries compared to other age groups, except for Norway where the proportion was higher among adults aged 65–74 years (Table 4). In the 28 EU countries, 91.7% of all adult RSV-associated hospital admissions occurred in adults ≥65 years of age (Table 4).

Importantly, the 2 model outputs did not differ substantially between the nearest-neighbor matching and multiple imputations approaches using the 2 indicator sets. The model only slightly differed by age group and the multiple imputation model estimates were slightly higher than the nearest-neighbor matching models.

Rate of RSV-Associated Hospital Admissions per Age Group and Across 28 EU Countries

The average annual RSV-associated hospital admission rates and numbers varied across the EU (Figure 2). The estimated rate of hospitalization was higher for adults ≥85 years (2.99 [95% CI, 2.56–3.42] per 1000) with an average number of hospital admissions of 37 904 (95% CI, 32 444–43 363) per year. Persons aged 18–64 years had the lowest hospitalization rate of 0.04 (95% CI, .03–.05 per 1000 per year) and average annual hospitalizations of 13 127 (95% CI, 10 904–15 350).

The highest hospital admission rate per 1000 adults aged 18–64 years (0.07 [95% CI, .06–.09]) was estimated in Ireland; the highest rates per 1000 adults aged 65–74 years (1.37 [95% CI, 1.18–1.57]), 75–84 years (2.59 [95% CI, 2.29–2.88]), and ≥85 years (4.45 [95% CI, 3.61–5.28]) were estimated for Norway, Bulgaria, and Romania, respectively. The lowest hospital admission rates per 1000 adults aged 18–64 years (0.01 [95% CI, −.00 to .02]), 65–74 years (0.09 [95% CI, −.09 to .27]), and ≥85 years (1.12 [95% CI, .28–1.96]) were estimated in Finland, while the lowest hospital admission rate in adults aged 75–84 years (1.53 [95% CI, 1.23–1.83] per 1000) was estimated in the Netherlands (Table 3).

DISCUSSION

RSV infection among older adults, especially those with underlying health conditions, is an important cause of ARIs that can lead to hospitalization. A previous multisite RSV burden cohort study conducted among healthy older adults and adults with comorbidities in 3 European countries showed that RSV burden in both healthy older adults and adults with comorbidities is substantial and comparable to that of influenza [17].

These estimates of RSV-associated hospitalizations in older adults are the first analysis integrating available data in 6 European countries to provide empirical evidence of the disease burden in this population across the EU. Our estimates

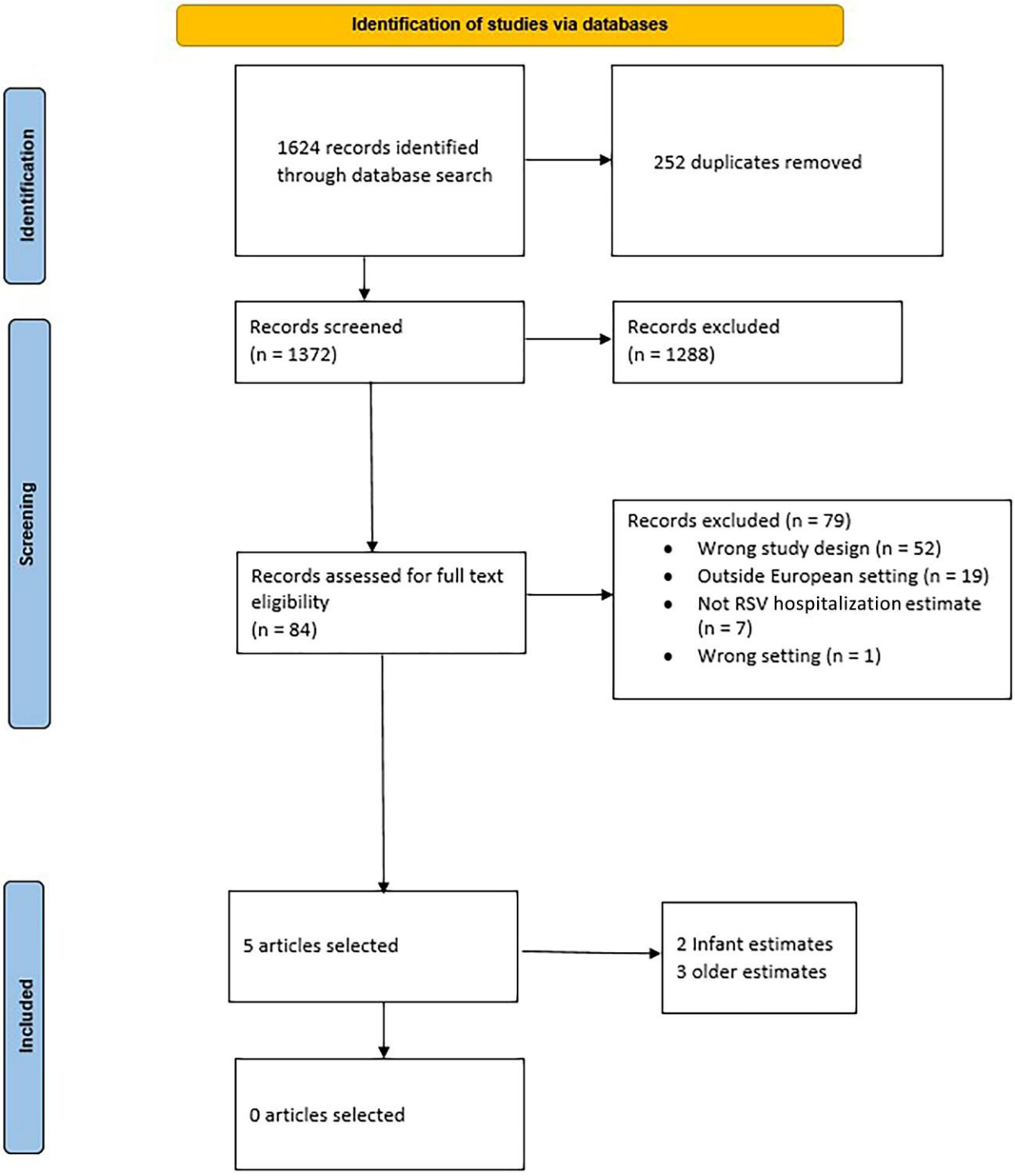

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart outlining the search records of respiratory syncytial virus (RSV)–associated hospitalization estimates in European countries.

show that RSV causes a high annual number of hospital admissions in adults across the EU (roughly 160 000 per year) with about 92% of cases occurring in adults aged ≥65 years. The highest annual count of RSV-associated hospitalizations occurred among adults aged 75–84 years and the highest rate of RSV-associated hospital admissions occurred among adults >85 years of age. It is important to note that for a condition that was considered in the past to be primarily a disease of young children, the average RSV-associated hospitalization estimate in adults was lower, but of a similar magnitude to that in

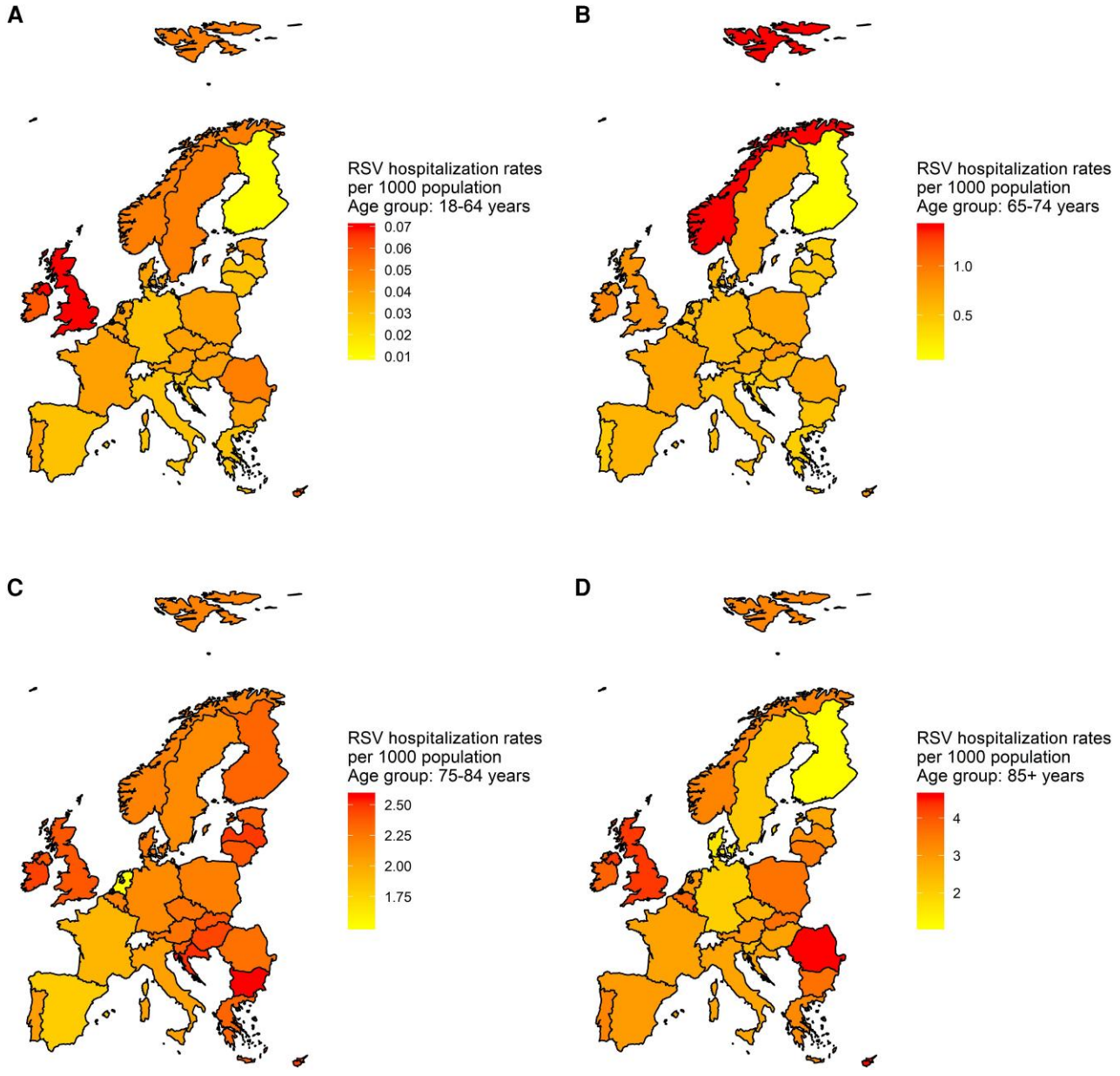

Figure 2. Respiratory syncytial virus (RSV)–associated hospitalization rates per 1000 population in 28 European Union countries and Norway, in adults aged 18–64 years (*A*), 65–74 years (*B*), 75–84 years (*C*), and ≥85 years (*D*).

children aged 0–4 years: 158 229 (95% CI, 140 865–175 592) versus 245 244 (95% CI, 224 688–265 799) hospitalizations per year [28]. Indeed, taking the estimates for children aged 0–4 years into account, we estimate that 39% (145 604/371 299) of the annual number of RSV-associated hospitalizations in the EU occurred in persons aged ≥65 years. With the changing demographics across Europe where elderly populations are increasing in size and considering the fact that RSV hospitalization in adults can lead to acute functional decline and reduced quality of life [29], there is a need to obtain better data and estimates of the true burden of RSV in this age group.

Our estimates, based on the available data, suggest a high burden of RSV in terms of hospital admissions in adult populations. Several studies have previously reported the burden and severity of clinical outcomes of RSV among adults in different settings [7, 9, 10, 30–33]. For instance, in previous studies, the prevalence of RSV has been reported to be 2 times higher in patients aged >75 years compared to those aged <60 years [34]. Sundaram et al report that RSV is a major cause of acute respiratory infection in adults aged >50 years and that RSV infection is more frequently associated with adults aged 65–79 years when compared to those aged 50–64 years [35]. In a

Table 2. Estimated Average Annual Respiratory Syncytial Virus–Associated Hospitalizations by Age Group in 28 European Union Countries (Including the United Kingdom) and Norway

	Average Annual No. of Hospitalizations (95% CI), by Age Group				
Country	18–64 y	65–74 y	75–84 y	≥85 y	≥65 y
EU 28[a]	13 127 (10 904–15 350)	32 679 (27 594–37 764)	74 519 (69 923–79 115)	37 904 (32 444–43 363)	145 102 (129 961–160 242)
Austria	202 (132–272)	587 (433–740)	1155 (1002–1309)	614 (434–795)	2356 (1869–2844)
Belgium	332 (244–420)	638 (456–820)	1608 (1396–1820)	1094 (852–1335)	3340 (2704–3975)
Bulgaria	207 (149–265)	494 (346–641)	1253 (1110–1396)	412 (308–516)	2159 (1764–2553)
Croatia	94 (60–127)	222 (146–296)	737 (648–825)	213 (151–275)	1172 (945–1396)
Cyprus	34 (27–41)	55 (42–68)	100 (88–112)	46 (36–56)	201 (166–236)
Czech Republic	305 (220–391)	736 (530–941)	1252 (1091–1413)	526 (374–678)	2514 (1995–3032)
Denmark	138 (94–181)	396 (284–509)	675 (584–767)	188 (89–287)	1259 (957–1563)
Estonia	35 (24–45)	62 (40–85)	207 (180–234)	84 (59–108)	353 (279–427)
Finland	26 (−16 to 68)	55 (−56 to 166)	795 (693–896)	150 (38–262)	1000 (675–1324)
France	1637 (1153–2121)	4244 (3172–5316)	7662 (6471–8854)	5901 (4258–7543)	17 807 (13 901–21 713)
Germany	1393 (746–2040)	5387 (3885–6889)	13 843 (11 923–15 764)	4514 (2713–6314)	23 744 (18 521–28 967)
Greece	249 (164–334)	526 (331–721)	2133 (1876–2390)	967 (706–1227)	3626 (2913–4338)
Hungary	262 (181–342)	679 (498–859)	1332 (1163–1500)	512 (360–664)	2523 (2021–3023)
Ireland	214 (178–251)	322 (260–385)	459 (402–514)	224 (169–279)	1005 (831–1178)
Italy	1347 (876–1817)	3603 (2444–4762)	10 531 (9126–11 936)	4419 (2818–6021)	18 553 (14 388–22 719)
Latvia	43 (27–59)	108 (72–144)	341 (299–383)	135 (100–170)	584 (471–697)
Lithuania	56 (33–80)	159 (109–208)	482 (421–542)	231 (177–286)	872 (707–1036)
Luxembourg	21 (16–25)	43 (35–50)	59 (51–67)	39 (30–47)	141 (116–164)
Malta	12 (9–16)	37 (29–46)	58 (50–65)	20 (13–26)	115 (92–137)
Netherlands	429 (296–561)	1000 (689–1311)	1427 (1150–1704)	1040 (751–1328)	3467 (2590–4343)
Norway	158 (117–199)	651 (558–744)	515 (441–589)	393 (295–491)	1559 (1294–1824)
Poland	970 (645–1295)	2254 (1685–2823)	4445 (3851–5039)	2246 (1690–2802)	8945 (7226–10 664)
Portugal	252 (170–333)	543 (352–734)	1609 (1383–1835)	943 (712–1173)	3095 (2447–3742)
Romania	738 (576–900)	1422 (1100–1745)	2759 (2393–3125)	1430 (1162–1699)	5611 (4655–6569)
Slovakia	145 (98–191)	386 (305–466)	570 (501–639)	249 (189–308)	1205 (995–1413)
Slovenia	44 (27–61)	85 (51–120)	311 (272–350)	100 (64–137)	496 (387–607)
Spain	1031 (657–1405)	2509 (1742–3275)	5409 (4530–6288)	3217 (2133–4301)	11 135 (8405–13 864)
Sweden	285 (211–360)	681 (488–876)	1220 (1048–1392)	660 (445–875)	2561 (1981–3143)
United Kingdom	2896 (2039–3752)	4846 (2860–6832)	8625 (7034–10 216)	6002 (4028–7976)	19 473 (13 922–25 024)

Abbreviations: CI, confidence interval; EU, European Union.

[a]Includes United Kingdom and excludes Norway.

community cohort of adults aged ≥50 years, the incidence of medically attended RSV infection was found to increase with age and the highest incidence occurred among persons aged >70 years [36]. Our estimates of RSV-associated hospitalization rates are consistent with the most recent pooled estimates based on prospective surveillance and modeling from the United States, which report annual rates of RSV-associated hospitalization of 178 (95% CI, 152–204) per 100 000 adults aged ≥65 years [37]. Among adults aged ≥65 years in the United States, about 159 000 RSV-associated hospitalizations are estimated to occur each year, which is comparable to our estimates of >145 000 hospitalizations occurring in the same age group across the EU [37]. We have focused on RSV-associated hospital admissions in older adults, which are considered more severe, are expensive, and have quality of life implications [38], but we recognize that there is also a significant amount of RSV disease burden in the outpatient setting [39].

Our study had several important limitations. The national estimates used for the extrapolations were generated mainly from Northern and Western European countries. Additional national estimates from Southern and Eastern Europe would yield more representative and reliable estimates for the EU. The 2 sets of 10 indicators used to produce the extrapolations were selected based on their availability in all the countries included and are not (always) specific to RSV. Future estimates generated with this approach should attempt to use a more RSV-aligned set of indicators (eg, indoor and outdoor pollution, geographical and ecological factors, and economic level). The estimates used for stage 1 were based on the overall number of hospitalizations with respiratory infections along with weekly test positives from laboratory data. The number of admissions and positive tests differed between the included countries, and as such, the estimates are still affected by country- or age-specific coding practices. Our estimates may differ from other studies using a similar approach because the stage 1

Table 3. Estimated Rates of Annual Respiratory Syncytial Virus–Associated Hospitalizations by Age Group per 1000 Adults in 28 European Union Countries (including the United Kingdom) and Norway

	Rate of Hospitalization per 1000 Adults (95% CI), by Age Group			
Country	18–64 y	65–74 y	75–84 y	≥85 y
EU 28[a]	0.04 (.03–.05)	0.66 (.55–.76)	2.24 (2.10–2.38)	2.99 (2.56–3.42)
Austria	0.04 (.02–.05)	0.69 (.51–.87)	2.23 (1.94–2.53)	2.86 (2.02–3.70)
Belgium	0.05 (.04–.06)	0.62 (.45–.80)	2.23 (1.94–2.53)	3.79 (2.95–4.62)
Bulgaria	0.05 (.03–.06)	0.59 (.42–.77)	2.59 (2.29–2.88)	3.30 (2.46–4.14)
Croatia	0.04 (.02–.05)	0.53 (.35–.70)	2.46 (2.16–2.75)	2.87 (2.03–3.70)
Cyprus	0.06 (.05–.07)	0.76 (.58–.93)	2.53 (2.23–2.82)	3.94 (3.10–4.77)
Czech Republic	0.04 (.03–.06)	0.64 (.46–.82)	2.30 (2.00–2.59)	2.89 (2.05–3.72)
Denmark	0.04 (.03–.05)	0.63 (.45–.81)	2.19 (1.89–2.49)	1.60 (.76–2.44)
Estonia	0.04 (.03–.05)	0.49 (.31–.67)	2.28 (1.99–2.58)	2.87 (2.03–3.71)
Finland	0.01 (.00–.02)	0.09 (–.09 to .27)	2.32 (2.03–2.62)	1.12 (.28–1.96)
France	0.04 (.03–.06)	0.70 (.53–.88)	1.90 (1.60–2.19)	3.01 (2.18–3.85)
Germany	0.03 (.01–.04)	0.64 (.46–.82)	2.13 (1.83–2.42)	2.10 (1.26–2.94)
Greece	0.04 (.02–.05)	0.48 (.30–.66)	2.45 (2.15–2.74)	3.10 (2.27–3.94)
Hungary	0.04 (.03–.05)	0.67 (.49–.85)	2.33 (2.04–2.63)	2.82 (1.99–3.66)
Ireland	0.07 (.06–.09)	0.92 (.74–1.10)	2.42 (2.13–2.72)	3.37 (2.54–4.21)
Italy	0.04 (.02–.05)	0.55 (.38–.73)	2.21 (1.92–2.51)	2.31 (1.47–3.14)
Latvia	0.03 (.02–.05)	0.54 (.36–.71)	2.40 (2.11–2.70)	3.22 (2.38–4.05)
Lithuania	0.03 (.02–.04)	0.57 (.39–.75)	2.35 (2.05–2.64)	3.58 (2.75–4.42)
Luxembourg	0.06 (.04–.07)	1.02 (.84–1.20)	2.14 (1.84–2.44)	3.82 (2.99–4.66)
Malta	0.04 (.03–.06)	0.78 (.60–.96)	2.35 (2.05–2.65)	2.64 (1.80–3.49)
Netherlands	0.04 (.03–.05)	0.58 (.40–.76)	1.53 (1.23–1.83)	3.02 (2.18–3.86)
Norway	0.05 (.04–.06)	1.37 (1.18–1.57)	2.10 (1.80–2.41)	3.42 (2.56–4.27)
Poland	0.04 (.03–.05)	0.70 (.53–.88)	2.21 (1.91–2.51)	3.38 (2.54–4.21)
Portugal	0.04 (.03–.05)	0.51 (.33–.68)	2.10 (1.80–2.40)	3.43 (2.59–4.26)
Romania	0.06 (.05–.07)	0.78 (.61–.96)	2.22 (1.93–2.52)	4.45 (3.61–5.28)
Slovakia	0.04 (.03–.05)	0.85 (.68–1.03)	2.43 (2.13–2.72)	3.48 (2.65–4.32)
Slovenia	0.03 (.02–.05)	0.44 (.26–.62)	2.37 (2.07–2.66)	2.32 (1.48–3.15)
Spain	0.03 (.02–.05)	0.58 (.40–.76)	1.82 (1.52–2.11)	2.48 (1.65–3.32)
Sweden	0.05 (.04–.06)	0.63 (.45–.81)	2.11 (1.81–2.41)	2.58 (1.74–3.42)
United Kingdom	0.07 (.05–.09)	0.77 (.46–1.09)	2.31 (1.89–2.74)	3.95 (2.65–5.25)

Abbreviations: CI, confidence interval; EU, European Union.

[a]Includes United Kingdom and excludes Norway.

results used depended on overall, non-age-specific virology data and the regression models were built with seasonal trends and polynomials [22]. It would be useful to provide estimates by year, as has been done for influenza-associated respiratory mortality for the EU [40], to assess temporal trends in RSV-associated hospitalizations and to produce more recent estimates to better understand how the coronavirus disease 2019 pandemic has influenced RSV activity and its burdens such as infections, hospitalizations, and deaths.

There is also much uncertainty due to low proportions of cases tested for RSV. These uncertainties may be mitigated only by using the observed number of admissions with a specific diagnosis or with laboratory confirmation of diagnosis (all cases tested), and lower sensitivity of testing methods in this age group are improved by combining polymerase chain reaction and serology. With RSV, the reported burden of disease is broadly considered too low, a problem attributed to suboptimal sensitivity of RSV diagnostic testing from clinical specimen or type of diagnostic test used [16], low levels of RSV testing among hospitalized adults [13], and imperfect reporting of hospitalization *ICD-10* codes [14, 15]. In addition, routine diagnostic testing may not be appropriate for adults with RSV due to lower viral loads in adults compared to children [31, 41]. While the estimated burden of disease might be generally more uncertain, the high proportion of RSV-associated hospital admissions is more likely to reflect the overall healthcare burden and daily experiences of clinical professionals. The difference may even be larger in the elderly as this group is more often hospitalized due to other respiratory reasons than RSV and testing for RSV is probably done in only a limited number of elderly patients.

We have based this work on regression model estimates (which are not so dependent on high levels of RSV testing) to increase the comparability of the stage 1 estimates [42] and to limit the risk of underestimating the RSV disease burden in adults (as there is less testing in this age group) [13, 16].

Table 4. Proportion (%) of Overall Respiratory Syncytial Virus–Associated Hospitalizations Occurring in Adults Aged 18–64 Years, 65–74 Years, 75–84 Years, and ≥85 Years in the European Union and in Each Country

	Age Group				
Country	18–64 y	65–74 y	75–84 y	≥85 y	≥65 y
EU 28[a]	8.3	20.7	47.1	24.0	91.7
Austria	7.9	22.9	45.2	24.0	92.1
Belgium	9.0	17.4	43.8	29.8	91.0
Bulgaria	8.7	20.9	53.0	17.4	91.3
Croatia	7.4	17.5	58.2	16.8	92.6
Cyprus	14.5	23.4	42.6	19.6	85.5
Czech Republic	10.8	26.1	44.4	18.7	89.2
Denmark	9.9	28.3	48.3	13.5	90.1
Estonia	9.0	16.0	53.4	21.6	91.0
Finland	2.5	5.4	77.5	14.6	97.5
France	8.4	21.8	39.4	30.3	91.6
Germany	5.5	21.4	55.1	18.0	94.5
Greece	6.4	13.6	55.0	25.0	93.6
Hungary	9.4	24.4	47.8	18.4	90.6
Ireland	17.6	26.4	37.7	18.4	82.4
Italy	6.8	18.1	52.9	22.2	93.2
Latvia	6.9	17.2	54.4	21.5	93.1
Lithuania	6.0	17.1	51.9	24.9	94.0
Luxembourg	13.0	26.5	36.4	24.1	87.0
Malta	9.4	29.1	45.7	15.7	90.6
Netherlands	11.0	25.7	36.6	26.7	89.0
Norway	9.2	37.9	30.0	22.9	90.8
Poland	9.8	22.7	44.8	22.7	90.2
Portugal	7.5	16.2	48.1	28.2	92.5
Romania	11.6	22.4	43.5	22.5	88.4
Slovakia	10.7	28.6	42.2	18.4	89.3
Slovenia	8.1	15.7	57.6	18.5	91.9
Spain	8.5	20.6	44.5	26.4	91.5
Sweden	10.0	23.9	42.9	23.2	90.0
United Kingdom	12.9	21.7	38.6	26.8	87.1

Abbreviation: EU, European Union.

[a]Includes United Kingdom and excludes Norway.

Considering that the review of the literature found no eligible recent studies, there is a need for more data from more countries to generate improved estimates with less uncertainty as the uncertainty intervals given here are falsely narrow and do not capture all sources of uncertainty.

The main strength of this work is that we have used national data from several countries in a single agreed analysis framework to estimate the RSV-associated hospital admission burden for the EU. Our estimates provide a key insight into the healthcare burden that may be associated with RSV infection and can be used to inform healthcare planning, priority setting, and resource allocation. Our results are important for public health policy and practice as these estimates may guide the development of RSV surveillance systems, provide baseline evidence for the introduction of future vaccines, and raise awareness to generate more granular data. With evidence from recent clinical trials showing that Ad26.RSV.preF–RSV preF protein vaccine is immunogenic and prevented RSV-mediated lower respiratory tract diseases in adults aged ≥65 years [43], this study highlights the burden in this population for prioritization for future vaccines. These data should therefore contribute to decision-making and policy formulation to improve relevant prevention, diagnostics, and healthcare service delivery for this population.

Supplementary Data

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

Notes

Acknowledgments. RESCEU investigators: Harish Nair (University of Edinburgh), Harry Campbell (University of Edinburgh), Philippe Beutels (Universiteit Antwerpen), Louis Bont (University Medical Center Utrecht), Andrew Pollard (University of Oxford), Peter Openshaw (Imperial College London), Federico Martinon-Torres (Servicio Galego de Saude), Terho Heikkinen (University of Turku and Turku University Hospital), Adam Meijer (National Institute for Public Health and the Environment), Thea K. Fischer (Statens Serum Institut), Maarten van den Berge (University of Groningen), Carlo Giaquinto (PENTA Foundation), Michael Abram (AstraZeneca), Kena Swanson (Pfizer), Bishoy Rizkalla (GlaxoSmithKline), Charlotte Vernhes (Sanofi Pasteur), Scott Gallichan (Sanofi Pasteur), Jeroen Aerssens (Janssen), Veena Kumar (Novavax), and Eva Molero (Team-It Research).

Disclaimer. Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred. This work reflects only the authors' views and opinions. The European Commission is not responsible for any use that may be made of the information it contains.

Financial support. This work is part of RESCEU, which has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (grant agreement 116019). This joint undertaking receives support from the European Union's Horizon 2020 research and innovation program and European Federation of Pharmaceutical Industries and Associations. This publication only reflects the authors' views, and the joint undertaking is not responsible for any use that may be made of the information it contains herein. Funding to pay the Open Access publication charges for this article was provided by the University of Edinburgh.

Potential conflicts of interest. R. O.-Y. reports support from the Innovative Medicines Initiative (IMI)–funded PROMISE consortium. T. K. F. reports support from the IMI-funded PROMISE consortium and consulting fees from Pfizer as chairperson for European Congress of Clinical Microbiology and Infectious Diseases conference symposium on RSV infections among adults. M. B. is an employee of Sanofi Vaccines and may hold stock in the company. H. C. reports grants, personal fees, and nonfinancial support from the World Health Organization, grants and personal fees from Sanofi Pasteur, and grants from the Bill & Melinda Gates Foundation; all payments were made via the University of Edinburgh. H. C. is a shareholder in the Journal of Global Health Ltd. J. P. declares unrestricted grants from Sanofi to the Netherlands Institute for Health Services Research (Nivel) for research on RSV, influenza, and severe acute respiratory syndrome coronavirus 2. Nivel received a research grant from the University of Edinburgh for the submitted work. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized problem. Drugs Aging **2015**; 32:261–9.
2. Atamna A, Babich T, Froimovici D, Yahav D, Sorek N, Ben-Zvi H, et al. Morbidity and mortality of respiratory syncytial virus infection in hospitalized adults: comparison with seasonal influenza. Int J Infect Dis **2021**; 103:489–93.
3. Falsey AR, McElhaney JE, Beran J, van Essen GA, Duval X, Esen M, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. J Infect Dis **2014**; 209:1873–81.
4. Volling C, Hassan K, Mazzulli T, Green K, Al-Den A, Hunter P, et al. Respiratory syncytial virus infection–associated hospitalization in adults: a retrospective cohort study. BMC Infect Dis **2014**; 14:1471–2334.
5. 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 **2014**; 8:347–52.
6. Naorat S, Chittaganpitch M, Thamthitiwat S, Henchaichon S, Sawatwong P, Srisaengchai P, et al. Hospitalizations for acute lower respiratory tract infection due to respiratory syncytial virus in Thailand, 2008–2011. J Infect Dis **2013**; 208(Suppl 3):S238–45.
7. Lee N, Lui GC, Wong KT, Li TC, Tse EC, Chan JY, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis **2013**; 57:1069–77.
8. Pastula ST, Hackett J, Coalson J, Jiang X, Villafana T, Ambrose C, et al. Hospitalizations for respiratory syncytial virus among adults in the United States, 1997–2012. Open Forum Infect Dis **2017**; 4:ofw270.
9. Loubet P, Lenzi N, Valette M, Foulongne V, Krivine A, Houhou N, et al. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. Clin Microbiol Infect **2017**; 23:253–9.
10. Branche AR, Saiman L, Walsh EE, Falsey AR, Sieling WD, Greendyke W, et al. Incidence of respiratory syncytial virus infection among hospitalized adults, 2017–2020. Clin Infect Dis **2022**; 74:1004–11.
11. 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 **2020**; 148:e48.
12. Shi T, Denouel A, Tietjen AK, Campbell I, Moran E, Li X, 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. J Infect Dis **2020**; 222(Suppl 7):S577–83.
13. Rozenbaum MH, Judy J, Tran D, Yacisin K, Kurosky SK, Begier E. Low levels of RSV testing among adults hospitalized for lower respiratory tract infection in the United States. Infect Dis Ther **2023**; 12:677–85.
14. Cai W, Tolksdorf K, Hirve S, Schuler E, Zhang W, Haas W, et al. Evaluation of using *ICD-10* code data for respiratory syncytial virus surveillance. Influenza Other Respir Viruses **2020**; 14:630–7.
15. Hamilton MA, Calzavara A, Emerson SD, Djebli M, Sundaram ME, Chan AK, et al. Validating *International Classification of Disease 10th Revision* algorithms for identifying influenza and respiratory syncytial virus hospitalizations. PLoS One **2021**; 16:e0244746.
16. Onwuchekwa C, Moreo LM, Menon S, Machado B, Curcio D, Kalina W, et al. Under-ascertainment of respiratory syncytial virus infection in adults due to diagnostic testing limitations: a systematic literature review and meta-analysis. J Infect Dis **2023**; 228:173–184.
17. Korsten K, Adriaenssens N, Coenen S, Butler C, Ravanfar B, Rutter H, et al. Burden of respiratory syncytial virus infection in community-dwelling older adults in Europe (RESCEU): an international prospective cohort study. Eur Respir J **2021**; 57:2002688.
18. Hansen CL, Chaves SS, Demont C, Viboud C. Mortality associated with influenza and respiratory syncytial virus in the US, 1999–2018. JAMA Netw Open **2022**; 5:e220527.
19. Allen JC, Toapanta FR, Chen W, Tennant SM. Understanding immunosenescence and its impact on vaccination of older adults. Vaccine **2020**; 38:8264–72.

20. Yarnall AJ, Sayer AA, Clegg A, Rockwood K, Parker S, Hindle JV. New horizons in multimorbidity in older adults. Age Ageing **2017**; 46:882–8.
21. Falsey AR. Editorial commentary: respiratory syncytial virus: a global pathogen in an aging world. Clin Infect Dis **2013**; 57:1078–80.
22. Johannesen CK, van Wijhe M, Tong S, Fernandez LV, Heikkinen T, van Boven M, et al. Age-specific estimates of respiratory syncytial virus–associated hospitalizations in 6 European countries: a time series analysis. J Infect Dis **2022**; 226:S29–37.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ **2021**; 372:n71.
24. Simonsen L, Spreeuwenberg P, Lustig R, Taylor RJ, Fleming DM, Kroneman M, et al. Global mortality estimates for the 2009 influenza pandemic from the GLaMOR project: a modeling study. PLoS Med **2013**; 10: e1001558.
25. Mangtani P, Hajat S, Kovats S, Wilkinson P, Armstrong B. The association of respiratory syncytial virus infection and influenza with emergency admissions for respiratory disease in London: an analysis of routine surveillance data. Clin Infect Dis **2006**; 42:640–6.
26. Müller-Pebody B, Crowcroft NS, Zambon MC, Edmunds WJ. Modelling hospital admissions for lower respiratory tract infections in the elderly in England. Epidemiol Infect **2006**; 134:1150–7.
27. Sharp A, Minaji M, Panagiotopoulos N, Reeves R, Charlett A, Pebody R. Estimating the burden of adult hospital admissions due to RSV and other respiratory pathogens in England. Influenza Other Respir Viruses **2022**; 16:125–31.
28. Del Riccio M, Spreeuwenberg P, Osei-Yeboah R, Klint Johannesen C, Vazquez Fernandez L, Teirlinck A, et al. Defining the burden of disease of RSV in Europe: estimates of RSV-associated hospitalisations in children under 5 years of age. A systematic review and modelling study. J Infect Dis **2023**; 228:1528–38.
29. Branche AR, Saiman L, Walsh EE, Falsey AR, Jia H, Barrett A, et al. Change in functional status associated with respiratory syncytial virus infection in hospitalized older adults. Influenza Other Respir Viruses **2022**; 16:1151–60.
30. Boattini M, Almeida A, Christaki E, Marques TM, Tosatto V, Bianco G, et al. Severity of RSV infection in southern European elderly patients during two consecutive winter seasons (2017–2018). J Med Virol **2021**; 93:5152–7.
31. Talbot HK, Belongia EA, Walsh EE, Schaffner W. Respiratory syncytial virus in older adults: a hidden annual epidemic. Infect Dis Clin Pract **2016**; 24:295–302.
32. Fleming DM, Taylor RJ, Lustig RL, Schuck-Paim C, Haguinet F, Webb DJ, et al. Modelling estimates of the burden of respiratory syncytial virus infection in adults and the elderly in the United Kingdom. BMC Infect Dis **2015**; 15:443.
33. Colosia AD, Yang J, Hillson E, Mauskopf J, Copley-Merriman C, Shinde V, et al. The epidemiology of medically attended respiratory syncytial virus in older adults in the United States: a systematic review. PLoS One **2017**; 12:e0182321.
34. Bruyndonckx R, Coenen S, Butler C, Verheij T, Little P, Hens N, et al. Respiratory syncytial virus and influenza virus infection in adult primary care patients: association of age with prevalence, diagnostic features and illness course. Int J Infect Dis **2020**; 95:384–90.
35. Sundaram ME, Meece JK, Sifakis F, Gasser RA Jr, Belongia EA. Medically attended respiratory syncytial virus infections in adults aged >/= 50 years: clinical characteristics and outcomes. Clin Infect Dis **2014**; 58:342–9.
36. McClure DL, Kieke BA, Sundaram ME, Simpson MD, Meece JK, Sifakis F, et al. Seasonal incidence of medically attended respiratory syncytial virus infection in a community cohort of adults ≥50 years old. PLoS One **2014**; 9:e102586.
37. McLaughlin JM, Khan F, Begier E, Swerdlow DL, Jodar L, Falsey AR. Rates of medically attended RSV among US adults: a systematic review and meta-analysis. Open Forum Infect Dis **2022**; 9:ofac300.
38. Rafferty E, Paulden M, Buchan SA, Robinson JL, Bettinger JA, Kumar M, et al. Evaluating the individual healthcare costs and burden of disease associated with RSV across age groups. Pharmacoeconomics **2022**; 40:633–45.
39. Belongia EA, King JP, Kieke BA, Pluta J, Al-Hilli A, Meece JK, et al. Clinical features, severity, and incidence of RSV illness during 12 consecutive seasons in a community cohort of adults ≥60 years old. Open Forum Infect Dis **2018**; 5:ofy316.
40. Paget J, Danielle Iuliano A, Taylor RJ, Simonsen L, Viboud C, Spreeuwenberg P, et al. Estimates of mortality associated with seasonal influenza for the European Union from the GLaMOR project. Vaccine **2022**; 40:1361–9.
41. Coultas JA, Smyth R, Openshaw PJ. Respiratory syncytial virus (RSV): a scourge from infancy to old age. Thorax **2019**; 74:986–93.
42. Paget J, Staadegaard L, Wang X, Li Y, van Pomeren T, van Summeren J, et al. Global and national influenza-associated hospitalisation rates: estimates for 40 countries and administrative regions. J Glob Health **2023**; 13:04003.
43. Falsey AR, Williams K, Gymnopoulou E, Bart S, Ervin J, Bastian AR, et al. Efficacy and safety of an Ad26.RSV.preF–RSV preF protein vaccine in older adults. N Engl J Med **2023**; 388:609–20.