Estimation of the number of RSV-associated hospitalisations in adults in the European Union

Title

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Running title: RSV hospitalisations in adults in the EU

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Summary of article's main point

RSV causes a high annual number of hospital admissions in adults across the EU (roughly 160 000 per year). About 92% of these admissions occur in adults aged 65 years and above.

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Abstract

Background: Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections in older adults that can result in hospitalisations and death. Estimating RSV-associated hospitalisation is critical for planning RSV-related healthcare needs for the ageing population across Europe.

Methods: We gathered national RSV-associated hospitalisation estimates from the REspiratory Syncytial virus Consortium in EUrope (RESCEU) for adults in Denmark, England, Finland, Norway, Netherlands, and Scotland from 2006 to 2017. We extrapolated these estimates to 28 EU countries using nearest-neighbour matching, multiple imputations, and two sets of 10 indicators.

Results: On average, 158 229 (95%CI: 140 865-175 592) RSV-associated hospitalisations occur annually among adults in the EU (above 18 years); 92% of these hospitalisations occur in adults over 65 years. Among 75-84 years old, 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 adults. Among adults aged ≥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).

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

Keywords

Respiratory syncytial virus, adults, hospitalisation, European Union, burden

Introduction

Respiratory syncytial virus (RSV) is a major cause of acute respiratory infections (ARI) 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 hospitalisation 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-immunised populations, have been reported in hospitalised adults [2]. The mean length of hospitalisation 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 (6-25 days) has been reported in adults hospitalised with RSV [9].

A high burden of RSV hospitalisations 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 hospitalised adults [5, 11, 12]. Estimating the incidence of RSV infection in hospitalised adults remains challenging as there are no dedicated RSV surveillance systems, low levels of routine testing of RSV in patients with an ARI [13] and only the more severe cases are commonly diagnosed. Other challenges include imperfect reporting of hospitalisation ICD-10 codes [14, 15] and diagnostic testing limitations [16]. A study conducted in three European countries across two seasons showed that RSV burden in community-dwelling older adults and adults with comorbidities is substantial and comparable to influenza but rarely caused severe diseases [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 (hCFR) 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 hospitalisations partly due to immunosenescence [19] and the number of comorbidities that exist in this population [20].

It is recognised that RSV infections are common in older adults in high-income countries [7, 21]. To effectively plan healthcare resource utilisation and adequately manage the RSV-related healthcare needs of the older adult population across Europe, including prioritising 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 UK and Norway by using data from a previously published REspiratory Syncytial virus Consortium in EUrope (RESCEU) study [22] and a literature review.

Methods

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

Stage 1 input data

In Stage 1, we gathered and used modelling inputs from the previously published RESCEU project estimating nationally RSV-associated average annual hospitalisations and

hospitalisation rates for adults in Denmark, England, Finland, Norway, Netherlands, and Scotland from 2006 to 2017 [22]. These studies used time-series regression methods to estimate the RSV-associated numbers and rates of hospitalisation.

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 pre-defined terms to identify original articles on RSV-associated hospitalisations (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 (ROY and MDR) 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 modelling

In Stage 2, we extracted the data from the six national RESCEU estimates to create the input data. We extrapolated the input data to the EU using two different modelling approaches: nearest-neighbour matching, multiple imputations, and two sets of 10 indicators (Supplementary File 2) [24]. The indicators were selected based on plausibility [24] and the availability of data in all included countries and are not always specific to RSV. The indicators only aim to capture variability across countries. Two sets of indicators were used in order to reduce bias and ensure more stable estimates were generated. This resulted in four distributions of plausible values for each country. The nearest neighbour 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 two sets of 10 selected indicators. Next, a hierarchical linear model was used to estimate a rate and confidence interval for each country. These approaches generated four sets of estimates, with confidence intervals and the averages of these estimates and the confidence intervals were reported. We estimated the average number of RSV-associated hospitalisations and the annual hospitalisation rates (per 1 000 adult population) by age group in the EU including the UK and Norway. The outputs of the two modelling approaches for the EU are presented in Supplementary Files 3-10.

Results

Scoping literature review

Of 1 392 citations assessed, five 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 three 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 hospitalisation 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 five EU countries and Norway to 28 EU countries (including the UK), we estimate that on average 158 229 (95% Confidence Interval (CI): 140 865 – 175 592) RSV-associated hospitalisations occurred annually among adults aged 18 years and older (Table 2). The highest average annual number of RSV-associated hospital admissions among adults aged 18-64 years: 2 896 (95% CI: 2 039 – 3 752), and ≥85 years: 6 002 (95% CI: 4 028 – 7 976) were estimated to occur in the UK whilst the highest average annual RSV-associated number of hospital admissions for adults aged 65-74 years: 5 387 (95% CI: 3 885 – 6 889) 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 occurs in Malta (Table 2). Of the overall RSV-associated hospital admissions, 145 102 (95%CI: 129 961- 160 242) occurred among adults older than 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 1 000 adults per year (Table 3). The highest proportion of RSV-associated hospitalisations (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 65-74 years (Table 4). In the 28 EU

186 countries, 91.7% of all adult RSV-associated hospital admissions occurred in adults older
187 than 65 years (Table 4).

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

192 *Rate of RSV-associated hospital admissions per age group and across 28 EU countries*
193 The average annual RSV-associated hospital admission rates and numbers varied across the
194 EU. The estimated rate of hospitalisation was higher for adults ≥85 years (2.99, 95% CI: 2.56-
195 3.42 per 1 000) with an average number of hospital admission of 37 904 (95%CI: 32 444 – 43
196 363) per year. Persons aged 18-64 years had the lowest hospitalisation rate of 0.04 (95% CI:
197 0.03-0.05 per 1 000 per year) and average annual hospitalisation of 13 127 (95% CI: 10 904 –
198 15 350).

199 The highest hospital admission rate per 1 000 adults aged 18-64 years [0.07 (95% CI: 0.06 -
200 0.09)] was estimated in Ireland; the highest rates per 1 000 adults aged 65-74 years [1.37
201 (95% CI: 1.18 - 1.57)], 75-84 years [2.59 (95% CI: 2.29 - 2.88)] and ≥85 years [4.45 (95% CI:
202 3.61 - 5.28)] were estimated for Norway, Bulgaria and Romania respectively. The lowest
203 hospital admission rates per 1 000 adults aged 18-64 years [0.01 (95% CI: -.00 - 0.02)], 65-74
204 years [0.09 (95% CI: -.09 - 0.27)] and ≥85 years [1.12 (95% CI: 0.28 - 1.96)] were estimated in
205 Finland, whilst the lowest hospital admission rate in adults aged 75-84 years [1.53 (95% CI:
206 1.23 - 1.83) per 1 000] was estimated in the Netherlands (Table 3).

207

Discussion

RSV infection among older adults, especially those with underlying health conditions, is an important cause of acute respiratory infections that can lead to hospitalisation. A previous multi-site RSV burden cohort study conducted among healthy older adults and adults with comorbidities in three European countries showed that RSV burden in both healthy older adults and adults with comorbidities is substantial and comparable to influenza [17].

These estimates of RSV-associated hospitalisations in older adults are the first analysis integrating available data in six European countries to provide empirical evidence of the disease burden in this population across the EU. Our estimates 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 and older. The highest annual count of RSV-associated hospitalisations occurred among adults aged 75-84 years and the highest rate of RSV-associated hospital admissions occurred among adults over 85 years. It is important to note that for a condition which was considered in the past to be primarily a disease of young children, the average RSV-associated hospitalisation estimate in adults was lower, but of a similar magnitude to that in children aged 0-4 years: 158 229 (95%CI: 140 865 – 175 592) versus 245 244 (95%CI: 224 688 – 265 799) hospitalisations per year [28]. Indeed, taking the estimates for children aged 0-4 years into account; we estimate that 39% (145 604 out of 371 299) of the annual number of RSV-associated hospitalisations in the EU occurred in persons aged 65 years and older. With the changing demographics across Europe where elderly populations are increasing in size and considering the fact that RSV hospitalisation in adults can lead to acute functional decline and reduced quality of life [29], there is a need to get better data and estimates of the true burden of RSV in this age group.

231 Our estimates, based on the available data, suggest a high burden of RSV in terms of
232 hospital admissions in adult populations. Several studies have previously reported the
233 burden and severity of clinical outcomes of RSV among adults in different settings [7, 9, 10,
234 30-33]. For instance, in previous studies, the prevalence of RSV has been reported to be two
235 times higher in patients aged over 75 years compared to those aged below 60 years [34].
236 Sundaram et al. report that RSV is a major cause of acute respiratory infection in adults aged
237 over 50 years and RSV infection is more frequently associated with adults aged 65-79 years
238 when compared to those aged 50-64 years [35]. In a community cohort of adults aged 50
239 years and over, the incidence of medically attended RSV infection was found to increase
240 with age and the highest incidence occurred among persons aged over 70 years [36]. Our
241 estimates of RSV-associated hospitalisation rates are consistent with the most recent
242 pooled estimates based on prospective surveillance and modelling from the USA which
243 report annual rates of RSV-associated hospitalisation of 178 (152-204) per 100 000 adults
244 aged ≥65 years [37]. Among adults aged ≥65 years in the US, about 159 000 RSV-associated
245 hospitalisations are estimated to occur each year which is comparable to our estimates of
246 over 145 000 hospitalisations occurring in the same age group across the EU [37]. We have
247 focused on RSV-associated hospital admission in older adults which is considered more
248 severe, expensive and has quality of life implications [38], but recognise that there is also a
249 significant amount of RSV disease burden in the outpatient setting [39].

250 Our study had several important limitations. The national estimates used for the
251 extrapolations were generated mainly from Northern and Western European countries.
252 Additional national estimates from Southern and Eastern Europe would yield more
253 representative and reliable estimates for the EU. The two sets of ten indicators used to
254 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 (e.g., indoor and outdoor pollution, geographical and ecological factors, and economic level). The estimates used for Stage 1 were based on the overall number of hospitalisations 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 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 hospitalisations and to produce more recent estimates to better understand how the COVID-19 pandemic has influenced RSV activity and its burdens such as infections, hospitalisations, and deaths.

There is also a lot of 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 if laboratory confirmation of diagnosis (all cases tested), and lower sensitivity of testing methods in this age group are improved by combining polymerase chain reaction (PCR) 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 hospitalised adults [13], and imperfect reporting of hospitalisation 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 hospitalised 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]. 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 and above [43], this study highlights the burden in this population for prioritisation for future vaccines. These data should

302 therefore contribute to decision-making and policy formulation to improve relevant

303 prevention, diagnostics and healthcare service delivery for this population.

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
Johannesen etal., 2022	Denmark	2010-2017	0-2m, 3-5m, 6-11m, 1-2y, 3-4y, 5-17y,18-64y, 65-74y, 75-84y, 85+y	ICD-10: Acute upper respiratory tract infection (URTI) (J00, J02-06); Pneumonia & influenza (J09-18); Bronchiolitis and bronchitis (J20-21, J40); Unspecified LRTI (J22)
Johannesen et al., 2022	England	2007-2017		
Johannesen et al., 2022	Finland	2006-2016		
Johannesen et al., 2022	Netherlands	2013-2017		
Johannesen et al., 2022	Norway	2008-2017		
Johannesen et al., 2022	Scotland	2010-2016		

312 Table 2: Estimated average annual RSV-associated hospitalisations by age groups in 28 EU countries (including the UK) and Norway

	Average annual number of hospitalisations (95% confidence interval) per age group				
Country	**18-64 years**	**65-74 years**	**75-84 years**	**≥85 years**	**≥65 years**
EU 28*	13127 (10904, 15350)	32679 (27594, 37764)	74519 (69923, 79115)	37904 (32444, 43363)	145102 (129961, 160242)
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, 68)	55 (-56, 166)	795 (693, 896)	150 (38, 262)	1000 (675, 1324)
France	1637 (1153, 2121)	4244 (3172, 5316)	7662 (6471, 8854)	5901 (4258, 7543)	17807 (13901, 21713)
Germany	1393 (746, 2040)	5387 (3885, 6889)	13843 (11923, 15764)	4514 (2713, 6314)	23744 (18521, 28967)
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)	10531 (9126, 11936)	4419 (2818, 6021)	18553 (14388, 22719)
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, 10664)
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)	11135 (8405, 13864)
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, 10216)	6002 (4028, 7976)	19473 (13922, 25024)

313

314 *Includes United Kingdom and excludes Norway

Table 3: Estimated rates of annual RSV-associated hospitalisations by age groups per 1 000 adults in 28 EU countries (including the UK) and Norway

	Rate of hospitalisation per 1 000 adults (95% confidence interval) per age group			
Country	**18-64 years**	**65-74 years**	**75-84 years**	**≥85 years**
EU 28*	0.04 (0.03, 0.05)	0.66 (0.55, 0.76)	2.24 (2.10, 2.38)	2.99 (2.56, 3.42)
Austria	0.04 (0.02, 0.05)	0.69 (0.51, 0.87)	2.23 (1.94, 2.53)	2.86 (2.02, 3.70)
Belgium	0.05 (0.04, 0.06)	0.62 (0.45, 0.80)	2.23 (1.94, 2.53)	3.79 (2.95, 4.62)
Bulgaria	0.05 (0.03, 0.06)	0.59 (0.42, 0.77)	2.59 (2.29, 2.88)	3.30 (2.46, 4.14)
Croatia	0.04 (0.02, 0.05)	0.53 (0.35, 0.70)	2.46 (2.16, 2.75)	2.87 (2.03, 3.70)
Cyprus	0.06 (0.05, 0.07)	0.76 (0.58, 0.93)	2.53 (2.23, 2.82)	3.94 (3.10, 4.77)
Czech Republic	0.04 (0.03, 0.06)	0.64 (0.46, 0.82)	2.30 (2.00, 2.59)	2.89 (2.05, 3.72)
Denmark	0.04 (0.03, 0.05)	0.63 (0.45, 0.81)	2.19 (1.89, 2.49)	1.60 (0.76, 2.44)
Estonia	0.04 (0.03, 0.05)	0.49 (0.31, 0.67)	2.28 (1.99, 2.58)	2.87 (2.03, 3.71)
Finland	0.01 (0.00, 0.02)	0.09 (-.09, 0.27)	2.32 (2.03, 2.62)	1.12 (0.28, 1.96)
France	0.04 (0.03, 0.06)	0.70 (0.53, 0.88)	1.90 (1.60, 2.19)	3.01 (2.18, 3.85)
Germany	0.03 (0.01, 0.04)	0.64 (0.46, 0.82)	2.13 (1.83, 2.42)	2.10 (1.26, 2.94)
Greece	0.04 (0.02, 0.05)	0.48 (0.30, 0.66)	2.45 (2.15, 2.74)	3.10 (2.27, 3.94)
Hungary	0.04 (0.03, 0.05)	0.67 (0.49, 0.85)	2.33 (2.04, 2.63)	2.82 (1.99, 3.66)
Ireland	0.07 (0.06, 0.09)	0.92 (0.74, 1.10)	2.42 (2.13, 2.72)	3.37 (2.54, 4.21)
Italy	0.04 (0.02, 0.05)	0.55 (0.38, 0.73)	2.21 (1.92, 2.51)	2.31 (1.47, 3.14)
Latvia	0.03 (0.02, 0.05)	0.54 (0.36, 0.71)	2.40 (2.11, 2.70)	3.22 (2.38, 4.05)
Lithuania	0.03 (0.02, 0.04)	0.57 (0.39, 0.75)	2.35 (2.05, 2.64)	3.58 (2.75, 4.42)
Luxembourg	0.06 (0.04, 0.07)	1.02 (0.84, 1.20)	2.14 (1.84, 2.44)	3.82 (2.99, 4.66)
Malta	0.04 (0.03, 0.06)	0.78 (0.60, 0.96)	2.35 (2.05, 2.65)	2.64 (1.80, 3.49)
Netherlands	0.04 (0.03, 0.05)	0.58 (0.40, 0.76)	1.53 (1.23, 1.83)	3.02 (2.18, 3.86)
Norway	0.05 (0.04, 0.06)	1.37 (1.18, 1.57)	2.10 (1.80, 2.41)	3.42 (2.56, 4.27)
Poland	0.04 (0.03, 0.05)	0.70 (0.53, 0.88)	2.21 (1.91, 2.51)	3.38 (2.54, 4.21)
Portugal	0.04 (0.03, 0.05)	0.51 (0.33, 0.68)	2.10 (1.80, 2.40)	3.43 (2.59, 4.26)
Romania	0.06 (0.05, 0.07)	0.78 (0.61, 0.96)	2.22 (1.93, 2.52)	4.45 (3.61, 5.28)
Slovakia	0.04 (0.03, 0.05)	0.85 (0.68, 1.03)	2.43 (2.13, 2.72)	3.48 (2.65, 4.32)
Slovenia	0.03 (0.02, 0.05)	0.44 (0.26, 0.62)	2.37 (2.07, 2.66)	2.32 (1.48, 3.15)
Spain	0.03 (0.02, 0.05)	0.58 (0.40, 0.76)	1.82 (1.52, 2.11)	2.48 (1.65, 3.32)
Sweden	0.05 (0.04, 0.06)	0.63 (0.45, 0.81)	2.11 (1.81, 2.41)	2.58 (1.74, 3.42)
United Kingdom	0.07 (0.05, 0.09)	0.77 (0.46, 1.09)	2.31 (1.89, 2.74)	3.95 (2.65, 5.25)

*Includes United Kingdom and excludes Norway

Table 4: Proportion of overall RSV-associated hospitalisations occurring in adults aged 18-64 years, 65-74 years, 75-84 years and ≥85 years in the EU and in each country

Country	18-64 years	65-74 years	75-84 years	≥85 years	≥65 years
EU 28*	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

*Includes United Kingdom and excludes Norway

Figure 1: PRISMA flowchart outlining the search records of RSV-associated hospitalisation estimates in European countries.

Figure 2: RSV-associated hospitalisation rates per 1000 population in 28 EU countries and Norway. A: RSV-associated hospitalisation rates per 1 000 in adults aged 18-64 years. B: RSV-associated hospitalisation rates per 1 000 in adults aged 65-74 years. C: RSV-associated hospitalisation rates per 1 000 in adults aged 75-84 years. D: RSV-associated hospitalisation rates per 1 000 in adults aged ≥85 years.

Footnote Page

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Potential conflict of interests

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Reference

1. Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized problem. Drugs Aging. 2015;32(4):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(12):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(665):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(3):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(8):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(1):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(4):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(6):1004-11.
11. Tin Tin Htar M, Yerramalla MS, Moisi 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-S83.
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(2):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(6):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(1):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.
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(4).
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(2):e220527.

19. Allen JC, Toapanta FR, Chen W, Tennant SM. Understanding immunosenescence and its impact on vaccination of older adults. Vaccine. 2020;38(52):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(6):882-8.
21. Falsey AR. Editorial commentary: respiratory syncytial virus: a global pathogen in an aging world. Clin Infect Dis. 2013;57(8):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-S37.
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(11):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(5):640-6.
26. Muller-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(6):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(1):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. medRxiv [Preprint]. 2023.
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(6):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(8):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(6):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(8):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(3):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(7):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(7):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(6):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(12):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(9):1361-9.
41. Coultas JA, Smyth R, Openshaw PJ. Respiratory syncytial virus (RSV): a scourge from infancy to old age. Thorax. 2019;74(10):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(7):609-20.