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ORIGINAL RESEARCH

Estimated Incidence of Hospitalizations and Deaths Attributable to Respiratory Syncytial Virus Infections Among Adults in Germany Between 2015 and 2019

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ABSTRACT

Introduction: Respiratory syncytial virus (RSV) burden in adults is underestimated mainly due to unspecific symptoms and limited standard-of-care testing. We estimated the population-based incidence of hospitalization and mortality attributable to RSV among adults with and without risk factors in Germany.

Methods: Weekly counts of hospitalizations and deaths for respiratory, cardiovascular, and cardiorespiratory diseases were obtained (Statutory Health Insurance database, 2015–2019). A quasi-Poisson regression model was fitted to estimate the number of hospitalizations and deaths attributable to RSV as a function of periodic and aperiodic time trends, and viral activity while allowing for potential overdispersion. Weekly counts of RSV and influenza hospitalizations in children < 2 years and adults ≥ 60 years, respectively, were used as viral activity indicators. Models were stratified by age group and risk status (defined as presence of selected comorbidities).

Results: Population-based RSV-attributable hospitalization incidence rates were high among adults ≥ 60 years: respiratory hospitalizations (236–363 per 100,000 person-years) and cardiorespiratory hospitalizations (584–912 per 100,000 person-years). RSV accounted for 2–3% of all cardiorespiratory hospitalizations in this age group. The increase in cardiorespiratory

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hospitalization risk associated with underlying risk factors was greater in 18–44 year old persons (five to sixfold higher) than in ≥ 75 year old persons (two to threefold higher).
Conclusions: This is a first model-based study to comprehensively assess adult RSV burden in Germany. Estimated cardiorespiratory RSV hospitalization rates increased with age and were substantially higher in people with risk factors compared to those without risk factors. Our study indicates that RSV, like other respiratory viruses, contributes to both respiratory and cardiovascular hospitalizations. Effective prevention strategies are needed, especially among older adults ≥ 60 years and among adults with underlying risk factors.

Keywords: Modeling; Disease burden; Quasi-Poisson regression; Respiratory syncytial virus; Hospitalization; Mortality; Adults; Germany

Key Summary Points

Why carry out the study?

Respiratory syncytial virus (RSV) causes a substantial disease burden among adults, however disease incidence is underestimated mainly due to nonspecific symptoms and limited standard-of-care testing.

We estimated RSV-attributable hospitalizations and deaths, stratified by age and risk status, in Germany during 2015–2019 using a quasi-Poisson regression model.

What was learned from the study?

Estimated cardiorespiratory RSV hospitalization rates increased with age and were substantially higher in people with risk factors compared to those without risk factors, particularly among younger adults.

We found that RSV, like other respiratory viruses, contributes not only to respiratory but also cardiovascular hospitalizations and deaths.

Efficacious RSV vaccines could have a high public health impact in older adults and among those with underlying comorbidities.

INTRODUCTION

Respiratory syncytial virus (RSV) is one of the most widespread respiratory pathogens affecting all age groups, but specifically the youngest and oldest persons [1, 2]. In younger children, the clinical presentation ranges from a mild cold to severe lower respiratory tract infections (LRTIs), like bronchiolitis and bronchitis, as well as secondary bacterial infections causing pneumonia [1]. In adults, in addition to respiratory disease, RSV also can cause exacerbations of cardiorespiratory disease (e.g., congestive heart failure, arrythmia, ischemic heart disease, and chronic obstructive pulmonary disease [COPD]) [3–5]. Older adults (aged ≥ 60 years), potentially due to aging of the immune system (immunosenescence) and low level systemic inflammation (inflammaging) [6–9], and those with underlying comorbidities (e.g., immunocompromised and chronic cardiorespiratory diseases) are at higher risk of RSV-related severe outcomes [10–13]. Globally, an estimated 787,000 RSV-related hospitalizations are projected to occur annually in high-income countries among adults 65 years and older [14].

For the first time, RSV vaccines were recently licensed to prevent lower respiratory tract disease caused by RSV in adults ≥ 60 years [12, 15]. Yet, the incidence and clinical burden of RSV disease in adults are difficult to measure due to the lack of specific RSV symptomatology that could distinguish it from influenza and other respiratory viruses, limited standard-of-care RSV testing among adults, reduced sensitivity of diagnostic testing among adults [16, 17], poor RSV diagnostic capacity in many healthcare facilities, and low public and medical community awareness of RSV in adults [18–21]. Furthermore, data on RSV burden in people with underlying conditions are sparse [4, 21, 22].

Model-based approaches are used increasingly to assess RSV incidence [23–48] since these models can more accurately reflect the true disease burden in the population. For example, a recent US meta-analysis found

RSV-related incidence estimates based on RSV-specific International Classification of Diseases (ICD) codes only to be 1 to 5 per 100,000 person-years among persons aged 65 years and older, vastly underestimating results from model-based and prospective studies, which were more comparable (236 and 282 per 100,000 person-years, respectively) [49]. Time series models aim to estimate the extent to which a specific pathogen affects larger outcome categories. Applied to RSV, time series models relate the temporal variability of an indicator of a pathogen (e.g., week-to-week RSV disease case counts) to the variability in the all-cause outcome of which a portion are expected to be RSV-related (e.g., respiratory-illness hospitalizations). In doing so, they estimate the number of RSV-related events, including undiagnosed RSV-related events, which explains why time series model results are higher than those based only on laboratory confirmed cases when RSV testing is incomplete. In addition, other large seasonal contributors for such outcomes, in this case influenza, are also accounted for in the model.

In Germany, the contribution of RSV to hospitalizations and deaths in adults is largely unknown as prospective observational studies that have assessed RSV incidence are scarce, and RSV became a nationwide notifiable disease only in July 2023 [50–54]. Two RSV vaccines (GSK's RSV Arexvy vaccine and Pfizer's RSV Abrysvo vaccine) for adults aged ≥ 60 years are available in Germany since 2023.In 2024, market authorization of the third RSV vaccine is expected.

The present study aimed to retrospectively estimate RSV-attributable incidence of hospitalizations and mortality in adults in Germany by using a time series model-based approach, to help inform potential RSV vaccine programs. To more accurately estimate the RSV burden, we used data on respiratory, cardiovascular and cardiorespiratory diseases, as a portion of such outcomes are associated with RSV [4, 5, 55, 56].

METHODS

Study Design

This was an observational retrospective database analysis to estimate the RSV-attributable incidence rates based on hospitalizations and mortality data among adults in Germany using a quasi-Poisson regression model.

Data Sources

Data on hospitalizations and deaths (2015–2019) were obtained from the "Deutsche Analysedatenbank für Evaluation und Versorgungsforschung" database (DADB database), containing data from the Statutory Health Insurance (SHI) data on approximately 3.5 million insured people. Included participants were females and males aged 18 years or older. The DADB database has been found to be fairly representative of the German population, with similar age-gender and morbidity structure [57]. The study period of 2015–2019 was selected to avoid distortion of RSV epidemiology during pandemic of COVID-19 [58, 59].

All diagnoses were coded based on the German Modification (GM) of the ICD 10th revision (ICD-10-GM) [60]. Both primary and secondary diagnoses, reported in hospital discharge records, were considered. Three major disease outcomes were included: all respiratory diseases (any mention of ICD-10-GM codes: J00-J99), all cardiovascular diseases (any mention of ICD-10-GM codes: I00-I99), and all cardiorespiratory diseases (any mention of ICD-10-GM codes: I00-I99, J00-J99). We included cardiorespiratory diseases to ensure that a patient hospitalized for a respiratory disease and a cardiovascular disease during the same hospitalization episode was counted as one case (instead of two).

Hospitalization was defined as an overnight stay in the hospital and started with the admission date. Readmissions within 30 days are quite frequent after hospitalizations for heart failure, acute myocardial infarction, or pneumonia [61, 62]. Thus, to avoid overcounting of cases due to readmissions, hospitalizations that occurred for

the same outcome within 30 days of discharge were collapsed with the index hospitalization; otherwise, they were considered independent hospitalizations. As no national mortality data nor clinical data for the cause of death during hospitalization are available, we modeled RSV's contribution to mortality associated with cardiorespiratory hospitalizations (i.e., all-cause deaths within 28 days of the most recent cardiorespiratory hospital admission date, which includes in-hospital deaths). Other literature supports the selection of this mortality outcome because deaths within a month of an inpatient admission are frequently considered associated with the hospitalization [14, 63] and used as the numerator for case fatality rate.

Individuals were categorized into four age groups: 18–44, 45–59, 60–74, and ≥ 75 years. A cut-off of 60 years and above was selected because RSV vaccinations are approved for adults ≥ 60 years. Data on risk factors for RSV, defined as the presence of at least one comorbidity reported within one year before hospitalization or death, were also collected. Chronic conditions including cardiac, respiratory, liver and kidney disease as well as immunosuppression, neurological disorders and diabetes mellitus were considered risk factors [13] (the complete list of comorbidities is provided in Supplementary Table 1). As the risk factor literature for RSV among adults [11] is limited, risk factors for severe influenza infection were also included [64].

RSV and influenza have similar seasonal patterns and both contribute to the outcomes of interest, thus were included in the model as covariates. The indicator for the circulation of RSV was defined as a weekly number of RSV-related hospitalization counts (ICD-10-GM codes: B97.4, J21.0, J12.1, J20.5, J21.9) in children < 2 years. RSV circulation in children has been selected in multiple other model-based studies [18, 28, 65] and is a common approach due to more frequent testing and hospitalization and higher sensitivity of diagnostic tests in children than in adults [20, 66]. We included J21.9 (acute bronchiolitis, unspecified) because RSV is the leading cause of bronchiolitis in this age group, accounting for the majority of bronchiolitis hospitalizations [67–69]. Additionally, it serves as an indicator marking the start of the RSV season [67–71] and tracks RSV activity independently of RSV testing levels which vary across the year. The indicator for the circulation of influenza was defined as a weekly number of influenza-specific hospitalization counts (ICD-10-GM codes: J09, J10, J11) in adults ≥ 60 years [65].

Statistical Analysis

Time series data were aggregated by week and stratified by age and risk groups. For each stratum of interest (i.e., each age- and risk-specific subgroup), we fitted a quasi-Poisson regression model to associate the outcome with aperiodic and periodic time trends and circulation of RSV and influenza while allowing for potential overdispersion. The baseline aperiodic trend in the outcome of interest (i.e., respiratory, cardiovascular, or cardiorespiratory disease) was accounted for in the model through polynomial terms up to the fourth order, whereas the baseline periodic trend was accounted for by harmonic terms. In addition, circulation of RSV and influenza was represented in the model through respective viral indicators. Viral indicators were lagged to account for potential delays between the peak in viral indicator and the corresponding peak in occurrence of the outcomes of interest. The identity link function was used to reflect the most biologically plausible link between viral circulation and the outcomes of interest.

The quasi-Poisson regression model fitted to the weekly data is given by:

$$\text{Nr\_events}_t \sim \text{Poisson}(\lambda_t, \theta) \text{with}$$

$$\lambda_t = \beta_0 + \sum_{k=1}^{4} \beta_k \cdot t^k + \beta_5 \cdot \sin\left(\frac{2\pi.t}{52.143}\right) + \beta_6 \cdot \cos\left(\frac{2\pi.t}{52.143}\right) + \beta_7 \cdot \sin\left(\frac{4\pi.t}{52.143}\right) + \beta_8 \cdot \cos\left(\frac{4\pi.t}{52.143}\right) + \sum_{l=1}^{L} \beta_{(8+l)} \cdot VP_{l(t-m_l)},$$

where λ_t represents the expected number of events in week t with $t = 1, 2, 3, \ldots, T_w$ representing the running week index, T_w the total number of weeks in the study period, and θ the overdispersion parameter. Parameter β_0 is the

coefficient associated with the baseline number of events, β_1 to β_4 are coefficients associated with the aperiodic time trend, β_5 to β_8 are coefficients associated with the periodic time trend, and $\beta_{(8+l)}$ are coefficients associated with appropriately lagged activity of pathogen l ($VP_{l(t-m_l)}$) with $l = 1, \ldots, L$ where $L = 2$ (RSV and influenza), and $m_l = 0, 1, \ldots, M$ the pathogen-specific time lag where $M = 4$.

Each final model was built in a step-by-step manner. In the first step, a model containing only the periodic and aperiodic trends was fitted. When possible, the polynomial order was reduced (significance level 0.05). Next, the viral indicators were added to the model. All possible lags of the viral indicators not yet included in the model were considered for inclusion (one at a time). The lagged indicator with the highest test statistic was selected for inclusion in the model. This approach was chosen because it is biologically implausible for the viral pathogens (RSV and influenza) to protect against the outcomes of interest [37, 72]. This viral indicator selection procedure was repeated until all viral indicators were included in the final model.

The weekly number of events that were attributable to RSV was calculated as the difference between the total model-estimated number of events (using the final model) and the model-estimated number of events under the hypothetical absence of RSV circulation (by setting the parameter associated with the RSV indicator to zero). The yearly subgroup-specific number of RSV-attributable events was obtained by summing over the included weeks.

RSV-attributable proportions of each outcome (percentages of cases attributable to RSV) were calculated by dividing the yearly model-based age- and risk-specific number of RSV-attributable events by the age- and the risk-specific annual number of respective observed events (hospitalizations or deaths).

The yearly incidence rates of RSV-attributable events for each subgroup (age- and risk-specific) were obtained by dividing the annual model-based number of RSV-attributable events by the corresponding subgroup population at risk, which is expressed as the number of events per 100,000 person-years. The age- and risk-specific populations (used as denominators in calculating the incidence rates) were obtained from the DADB database. To extrapolate the incidence rates to the national level, correction factors were used to adjust for slightly younger population in DADB database than in overall German population. Residual bootstrapping was used to obtain confidence intervals. Age-specific incidence rates of RSV-attributable events are obtained after summing both numerator and denominator over the risk groups.

Data management and statistical analysis were performed in R with version 4.0.4. The detailed study protocol can be found at [73].

Ethical Considerations

This study used aggregated and anonymized data, therefore not requiring approval from Institutional Review Boards or Ethical Committees or informed consents from patients. The study was conducted in accordance with legal and regulatory requirements and research practices described in the Good Epidemiological Practice guidelines issued by the International Epidemiological Association [74].

RESULTS

Study Population

Between 2015 and 2019, there were a total of 1.16 million cardiorespiratory hospitalizations, 1.05 million cardiovascular, 0.4 million respiratory hospitalizations and 49,997 deaths occurring within 28 days of a cardiorespiratory hospital admission in adults aged 18 or above in the German DADB database (data not shown). People aged ≥ 60 years accounted for nearly 70% of hospitalizations and 90% of deaths.

Estimated RSV-Attributable Hospitalizations

Estimated age- and risk-stratified annual RSV-attributable incidence rates of respiratory, cardiovascular, and cardiorespiratory hospitalizations are presented in Table 1. Parameter estimates for the final quasi- Poisson regression models for respiratory hospitalizations in patients without

Table 1 Estimated annual incidence rate (IR) per 100,000 person-years of RSV-attributable hospitalizations and percentage (%) of all respective hospitalizations attributable to RSV infections in adults in Germany, 2015–2019

Age group (years)	2015		2016		2017		2018		2019	
	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%
RSV-attributable respiratory hospitalizations										
Adults without risk factors										
18–44	8.2 [0.0; 22.3]	1.2	9.1 [0.0; 24.8]	1.2	13.5 [0.0; 36.7]	1.8	9.4 [0.0; 25.7]	1.2	13.0 [0.0; 35.5]	1.8
45–59	11.3 [0.0; 25.5]	2.0	11.1 [0.0; 25.1]	1.9	17.2 [0.0; 38.9]	2.8	11.7 [0.0; 26.3]	2.0	16.7 [0.0; 37.6]	2.8
60–74	29.2 [0.0; 68.0]	2.8	25.6 [0.0; 59.6]	2.3	38.2 [0.0; 88.8]	3.6	23.7 [0.0; 55.1]	2.2	32.3 [0.0; 75.1]	3.0
≥ 75	287.4 [122.6; 442.3]	7.1	292.1 [124.6; 449.7]	6.7	380.4 [162.2; 585.6]	8.4	258.8 [110.4; 398.3]	6.1	354.9 [151.4; 546.3]	8.6
Adults with risk factors										
18–44	50.5 [1.2; 98.3]	2.2	48.7 [1.2; 94.9]	1.9	83.6 [2.0; 162.9]	3.1	55.7 [1.3; 108.7]	2.1	80.3 [1.9; 156.5]	3.1
45–59	61.5 [0.8; 123.9]	1.9	60.3 [0.8; 121.6]	1.7	92.5 [1.2; 186.3]	2.5	61.8 [0.8; 124.4]	1.7	88.1 [1.2; 177.4]	2.4
60–74	186.5 [71.9; 307.0]	2.4	176.0 [67.8; 289.7]	2.1	250.7 [96.6; 412.6]	3.0	159.6 [61.5; 262.7]	2.0	214.5 [82.6; 353.0]	2.7
≥ 75	739.0 [462.9; 1031.5]	3.5	731.1 [457.9; 1020.5]	3.2	930.9 [583.1; 1299.4]	4.1	621.9 [389.5; 868.0]	2.9	829.3 [519.5; 1157.6]	3.8
Overall[a]										
18–44	19.1	1.8	19.3	1.6	31.1	2.5	21.1	1.7	29.8	2.5
45–59	33.3	2.0	32.7	1.7	50.5	2.6	33.9	1.8	48.5	2.5
60–74	135.9	2.4	127.4	2.1	181.9	3.1	115.6	2.0	155.4	2.7
≥ 75	671.4	3.6	666.9	3.3	851.9	4.2	570.5	3.0	763.9	4.0
≥ 60[b]	274.1	3.0	269.4	2.7	362.8	3.7	236.4	2.5	315.3	3.4
RSV-attributable cardiovascular hospitalizations										
Adults without risk factors										
18–44	10.6 [0.0; 24.1]	1.6	10.1 [0.0; 23.1]	1.3	16.8 [0.0; 38.4]	2.2	11.2 [0.0; 25.5]	1.5	15.9 [0.0; 36.4]	2.1
45–59	56.3 [13.5; 100.7]	2.5	51.8 [12.4; 92.7]	2.0	84.2 [20.2; 150.6]	3.3	55.3 [13.2; 98.9]	2.2	80.4 [19.3; 143.9]	3.2
60–74	109.0 [0.0; 238.3]	1.7	95.5 [0.0; 208.7]	1.4	142.3 [0.0; 311.1]	2.1	88.2 [0.0; 192.9]	1.4	120.3 [0.0; 263.1]	1.9

Table 1 continued

Age group (years)	2015		2016		2017		2018		2019	
	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%
≥ 75	483.3 [42.6; 935.1]	2.1	452.6 [39.9; 875.7]	1.9	631.5 [55.7; 1221.9]	2.7	418.6 [36.9; 810.0]	1.9	583.3 [51.5; 1128.7]	2.7
Adults with risk factors										
18–44	48.4 [0.0; 102.1]	1.8	46.7 [0.0; 98.5]	1.5	80.2 [0.0; 169.1]	2.5	53.5 [0.0; 112.8]	1.6	77.1 [0.0; 162.5]	2.3
45–59	187.0 [11.3; 347.0]	2.0	183.5 [11.1; 340.4]	1.8	281.2 [16.9; 521.8]	2.7	187.8 [11.3; 348.5]	1.9	267.8 [16.1; 496.9]	2.6
60–74	704.8 [211.5; 1150.9]	2.9	621.1 [186.4; 1014.3]	2.4	927.4 [278.3; 1514.5]	3.6	573.7 [172.2; 936.9]	2.4	784.3 [235.3; 1280.8]	3.2
≥ 75	1231.6 [316.6; 2123.1]	1.9	1122.5 [288.6; 1935.0]	1.6	1531.2 [393.7; 2639.7]	2.3	996.8 [256.3; 1718.5]	1.6	1350.7 [347.2; 2328.5]	2.1
Overall[a]										
18–44	20.4	1.7	19.6	1.4	32.8	2.4	21.8	1.6	31.2	2.2
45–59	113.5	2.1	109.6	1.8	171.2	2.8	114.2	1.9	163.9	2.8
60–74	512.8	2.8	451.0	2.3	673.0	3.5	416.7	2.3	569.2	3.1
≥ 75	1119.5	1.9	1024.4	1.7	1402.0	2.4	915.1	1.6	1244.8	2.2
≥ 60[b]	681.7	2.4	612.9	2.0	884.6	2.9	558.2	1.9	759.0	2.6
RSV-attributable cardiorespiratory hospitalizations										
Adults without risk factors										
18–44	15.9 [0.0; 40.4]	1.2	15.2 [0.0; 38.7]	1.0	25.4 [0.0; 64.4]	1.7	16.8 [0.0; 42.7]	1.2	24.0 [0.0; 60.9]	1.7
45–59	59.8 [8.7; 108.5]	2.3	55.0 [8.0; 99.9]	1.9	89.4 [13.1; 162.2]	3.0	58.7 [8.6; 106.6]	2.0	85.4 [12.5; 155]	3.0
60–74	120.1 [0.0; 257.2]	1.7	105.2 [0.0; 225.2]	1.4	156.8 [0.0; 335.8]	2.2	97.2 [0.0; 208.2]	1.4	132.6 [0.0; 283.9]	2.0
≥ 75	505.9 [49.7; 978.4]	2.1	473.8 [46.5; 916.3]	1.9	661.0 [64.9; 1278.4]	2.8	438.2 [43.0; 847.4]	1.9	610.6 [60.0; 1180.9]	2.7
Adults with risk factors										
18–44	85.2 [0.0; 168.5]	1.9	82.2 [0.0; 162.6]	1.6	141.0 [0.0; 279.2]	2.7	94.1 [0.0; 186.2]	1.8	135.5 [0.0; 268.2]	2.5
45–59	220.9 [20.9; 405.7]	2.1	216.7 [20.5; 397.9]	1.8	332.1 [31.4; 609.9]	2.8	221.8 [21.0; 407.4]	1.9	316.3 [29.9; 580.9]	2.7
60–74	691.9 [219.3; 1137.6]	2.7	653.0 [206.9; 1073.6]	2.4	929.9 [294.7; 1529.0]	3.4	592.1 [187.6; 973.5]	2.3	795.5 [252.1; 1308.0]	3.1

Table 1 continued

Age group (years)	2015		2016		2017		2018		2019	
	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%	IR [95% CI]	%
≥ 75	1306.4 [371.1; 2207.0]	2.0	1190.7 [338.3; 2011.5]	1.7	1624.3 [461.4; 2743.9]	2.4	1057.4 [300.4; 1786.3]	1.6	1432.8 [407.0; 2420.4]	2.2
Overall[a]										
18–44	33.9	1.6	32.5	1.4	54.5	2.3	36.2	1.5	51.8	2.2
45–59	130.3	2.1	126.0	1.8	196.6	2.8	131.2	2.0	188.2	2.8
60–74	507.6	2.6	475.7	2.3	679.4	3.3	432.0	2.2	580.7	3.0
≥ 75	1186.5	2.0	1085.7	1.7	1485.9	2.4	969.9	1.6	1319.3	2.2
≥ 60[b]	694.3	2.3	647.8	2.0	911.5	2.9	584.1	1.9	787.0	2.6

CI confidence interval, *IR* incidence rate extrapolated to the national level

[a]Based on pooling of results for models fitted to adults with and without risk factors, thus confidence intervals are not provided

[b]Pooled data for age group ≥ 60 years are provided only for overall, as the correction factor for extrapolation to the national level was not available for people with and without risk factor

and with risk factors, can be consulted in Supplementary Table 2 and Supplementary Table 3, respectively. Parameter estimates for the remaining models can be obtained from the authors upon request.

Incidence rates varied across years, with the highest rates observed in 2017. In all age groups, the overall RSV-attributable incidence rates were highest for cardiorespiratory diseases, followed by cardiovascular and respiratory diseases alone (Table 1). The RSV-attributable hospitalization incidence rates increased with age, with the high rates observed among people ≥ 60 years (respiratory diseases: 236–363 per 100,000 person-years; cardiovascular diseases: 558–885 per 100,000 person-years; and cardiorespiratory diseases: 584–912 per 100,000 person-years). The overall rates of RSV-attributable cardiorespiratory hospitalizations in those ≥ 75 years were on average approximately 30-fold, eightfold, and twofold higher compared to estimated rates in the younger age groups 18–44, 45–59, and 60–74 years, respectively. Adults with underlying risk factors had substantially higher incidence rates than those without (Table 1), but the increase in cardiorespiratory hospitalization risk associated with risk factors decreased with age [five to sixfold increase (18–44 years) versus two to threefold increase (≥ 75 years)] (Table 2). Incidence rates in overall older adults and in older adults with risk factors were very similar.

The contribution of RSV to cardiorespiratory and cardiovascular hospitalizations was similar between people with and without risk factors and accounted for 2–4% of those hospitalizations. However, the relative contribution of RSV for respiratory hospitalizations was considerably higher in the oldest adults (≥ 75 years) without risk factors (6–9%) compared to people with risk factors (3–4%), but the incidence rates remained higher in people with risk factors.

A seasonal pattern of respiratory hospitalizations and good model fit were observed for all age groups and were particularly strong among oldest age groups with risk factors (Supplementary Fig. 1). The seasonal pattern was also observed for cardiovascular and cardiorespiratory hospitalizations; however it was not as pronounced as in respiratory hospitalizations (Supplementary Figs. 2, 3).

Estimated Post-hospitalization RSV-Attributable Deaths

After plotting the weekly mortality data in inpatients, seasonality was not observed for adults without risk factors regardless of the age group; hence, it was not modeled. Among adults with risk factors, data on the two youngest age groups were also unsuitable for modeling due to lack of seasonality. The seasonality and good model fit were observed only for two older age groups with risk factors (Supplementary Fig. 4). The estimated age-specific annual RSV-attributable mortality rates in those age groups are presented in Table 3.

As expected, the highest mortality rates of RSV-attributable deaths within 28 days of cardiorespiratory hospitalizations were observed in the oldest age group (≥ 75 years). The rates ranged from 154 to 219 deaths per 100,000 person-years (3–4% of all cardiorespiratory deaths). These rates were up to 20-fold higher compared to the mortality rates in the age group of 60–74 years, where post-hospitalization mortality rates were also substantial ranging from 8.3 to 12.8 deaths per 100,000 person-years and accounted for 0.9% to 1.3% of all cardiorespiratory deaths (Table 3).

Table 2 Ratio of RSV-attributable hospitalization incidence in people with risk factor versus in people without risk factor (incidence rate ratio, IRR), Germany, 2015–2019

Age group (years)	2015 IRR	2016 IRR	2017 IRR	2018 IRR	2019 IRR
RSV-attributable respiratory hospitalizations					
18–44	6.2	5.4	6.2	5.9	6.2
45–59	5.4	5.4	5.4	5.3	5.3
60–74	6.4	6.9	6.6	6.7	6.6
≥ 75	2.6	2.5	2.4	2.4	2.3
RSV-attributable cardiovascular hospitalizations					
18–44	4.6	4.6	4.8	4.8	4.8
45–59	3.3	3.5	3.3	3.4	3.3
60–74	6.5	6.5	6.5	6.5	6.5
≥ 75	2.5	2.5	2.4	2.4	2.3
RSV-attributable cardiorespiratory hospitalizations					
18–44	5.4	5.4	5.6	5.6	5.6
45–59	3.7	3.9	3.7	3.8	3.7
60–74	5.8	6.2	5.9	6.1	6.0
≥ 75	2.6	2.5	2.5	2.4	2.3

DISCUSSION

We report the first model-based estimates of RSV-related incidence rate for Germany in adults and indicate that RSV hospitalization incidence increases substantially with age and is high among older adults 60 years and older and in people with risk factors, including younger adults. Our findings indicate that RSV contributes notably not only to respiratory but also cardiovascular hospitalizations. Moreover, we have shown that a substantial burden of deaths following cardiorespiratory hospital admission can be attributed to RSV in older people. Incidence rates among older adults with risk factors and overall are similar due to the very high proportion of older adults with underlying risk factors on the population overall.

Our respiratory hospitalization estimates were higher than those reported based on extrapolated estimates of hospitalization rates from RSV Consortium in Europe [75]. However, they are consistent with previous model-based studies [18, 65] and also a recent US meta-analysis, which reported incidence rates of RSV-attributable hospitalizations of 18.8, 99.5, and 281.6 cases per 100,000 person-years in age groups 18–49, 50–64, and ≥ 65 years, respectively, for pooled prospective studies after adjustment for diagnostic testing based under-ascertainment [49]. A similar incidence rate was also reported by a recent global meta-analysis of prospective studies from high income countries in people aged ≥ 65 years (347 cases per 100,000 person-years when adjusted for under-ascertainment) [14]. The proportions of all respiratory infections attributable to RSV in our study (3–4%) are also similar to previous observational studies, which

Table 3 Estimated annual mortality rate per 100,000 person-years of RSV-attributable deaths within 28 days of cardiorespiratory hospitalization and percentage of all such deaths attributable to RSV infections in adults with risk factors in Germany, 2015–2019

Age group (years)	2015		2016		2017		2018		2019	
	MR [95% CI]	%	MR [95% CI]	%	MR [95% CI]	%	MR [95% CI]	%	MR [95% CI]	%
60–74	9.4 [0; 30.6]	1.0	9.6 [0; 31.3]	1.0	12.8 [0; 41.7]	1.3	8.3 [0; 27.2]	0.9	11.0 [0; 36.0]	1.3
≥ 75	174.3 [85.6; 267.6]	3.3	190.5 [93.5; 292.4]	3.3	218.8 [107.4; 335.9]	4.1	153.6 [75.4; 235.8]	2.9	203.6 [100.0; 312.6]	4.2
≥ 60[a]	57.2	2.6	63.4	2.6	75.7	3.3	52.0	2.3	68.6	3.3

CI confidence interval, *MR* mortality rate extrapolated to the national level, *NA* not available

[a]Collapsed data for age groups 60–74, ≥ 75 years. Data on 18–44 and 45–59 were not suitable for modeling, thus no estimates are provided

reported that 4–8% of symptomatic respiratory infections in adults age ≥ 60 years were caused by RSV [14, 63]. The relatively similar values from our model-based approach and prospective study estimates that have been adjusted for reduced sensitivity of nasal/nasopharyngeal swab PCR [16, 17] in adults provide support for the validity of our model structure.

The epidemiology of RSV was substantially impacted by the implementation of nonpharmaceutical interventions during the COVID-19 pandemic in 2020–2021. During that period, an unprecedented decline in RSV cases in both children and adults in Germany was observed [58, 59]. However, in 2021/2022, there was a sudden increase and subsequent decrease in hospitalizations in children. In contrast, adults in the same season experienced fewer RSV cases compared to the pre-pandemic period. In 2022/2023, the number of RSV cases in adults aligned with expectations in the strong season [59]. Thus, we believe that our pre-pandemic estimates still provide meaningful insight into the current RSV burden.

The estimated RSV-attributable cardiorespiratory mortality rates in people age ≥ 75 years with risk factors (154–219 deaths per 100,000 person-years) aligned with a previous study in the UK (176 deaths per 100,000 in high-risk population) [11], although our data are limited to deaths in the first 28 days following hospitalization. Our post-hospitalization mortality rate results for adults ≥ 60 years (52–76 deaths per 100,000 person-years) were higher than those obtained in the recent US study, where RSV-attributable cardiorespiratory deaths in people age ≥ 65 years were estimated as 31.9 deaths per 100,000 person-years [76]. This difference may have occurred because the US study reported a rate among all persons in that age group rather than limiting the analysis to those with risk factors for severe disease. Modeled incidence rates of RSV-attributable hospitalizations and deaths were notably high among older adults and in individuals with underlying diseases. A German hospital-based retrospective study comparing the severity of RSV, influenza and SARS-CoV-2 cases observed that the average age of RSV patients was older than that of SARS-CoV-2

and influenza A patients [19]. In that study, RSV infections in older adults were more severe than influenza infections, particularly affecting individuals with increased risk. Pre-existing comorbidities have been associated with more severe outcomes from RSV infection, including increased need for hospitalization, longer lengths of stay, and higher rates of intensive care unit admission and death [13, 45, 63].

In our study, the differences in estimated RSV-attributable respiratory hospitalization rates between individuals with and without risk factors were particularly marked in the groups aged 18–44, 45–59 and 60–74 years, where rates were higher up to sevenfold. In the age group ≥ 75 years the incidence rate ratio between people with risk factors and without decreased to 2–3. This observation is in line with findings from a study in the UK where RSV-attributable hospitalization rates in persons aged 50–64 and 65–74 years with risk factors were up to 11-fold higher compared to their counterparts without risk factors [18], and decrease to threefold in the age group ≥ 75 years. This might be related to the fact that older age attenuates the impact of underlying risk factors, likely due to immunosenescence increasing risk among older adults [77, 78]. This suggests that future prevention strategies should target adults with underlying risk conditions, including younger adults, as well as older adults regardless of risk status.

Cardiorespiratory diseases accounted for the highest RSV-attributable hospitalization incidence rate. RSV can cause cardiovascular manifestations through several mechanisms. It can induce inflammation or immune dysregulation [4, 55, 79], which in turn may lead to atherosclerosis and accumulation of lipids [80]. RSV has also been identified in myocardial tissue in a patient with myocarditis, suggesting that the virus may directly cause myocardial injury [4]. Although the RSV proportion of all cardiovascular events in our study was low (2%), the population burden can be substantial given that cardiovascular diseases remain the leading cause of adult morbidity and mortality worldwide [81]. This suggests that future RSV vaccine strategies may prevent cardiovascular hospitalizations, as shown for influenza vaccines [82, 83].

Our study was characterized by several strengths. Firstly, we included a database with representation from all geographic areas of Germany and used a broad outcome definition of respiratory and cardiovascular diseases to capture events potentially attributable to RSV. To estimate the total burden of RSV on both cardiovascular and respiratory hospitalizations, we looked at a separate cardiorespiratory outcome, which avoids double counting of cases. In addition, data on underlying conditions enabled the identification of subpopulations at higher risk of RSV infection in both the outcomes events and the underlying population. Finally, the quasi-Poisson regression model allowed us to account for overdispersion and adjust for the co-circulation of influenza while correcting for underlying time trends.

We also acknowledge several study limitations. Including only hospitalized cases underestimates community RSV since approximately 89–94% of all medically attended RSV episodes are seen in the outpatient setting [84, 85]. Although the incidence estimated by our model approach accounts somewhat for under-ascertainment, we were not able to quantify the extent of this under-ascertainment through a comparison with the recorded RSV-specific hospitalizations, as such data were not available. In addition, our models included viral indicators only for RSV and influenza, which implicitly assumed that these are the only pathogens that show a relevant association with the outcome of interest. However, even without explicitly modeling other potentially relevant pathogens, they are, to a great extent, indirectly accounted for in the model through the periodic component and the overdispersion parameter. Moreover, RSV-specific hospitalizations in children under 2 years as an indicator for RSV activity may not fully reflect viral activity in adults. Finally, while the SHI database is representative of the German population, there is a slight age distribution bias towards younger individuals. Thus, adjustments were made for age-specific incidence rates using correction factors, but similar correction factors for age- and risk-specific incidence rates were not available.

CONCLUSION

Our study demonstrated that in Germany RSV causes a considerable burden of hospitalizations and mortality among adults 60 years and older and younger adults with underlying comorbidities. Like other respiratory viruses such as influenza and SARS-CoV-2, RSV infection contributes to both respiratory and cardiovascular hospitalizations. Our study highlights the need to implement effective prevention strategies, especially among the most affected groups.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to restriction of data provider. Weekly hospitalization data were provided by the Gesundheitsforen Leipzig GmbH.

Declarations

Conflict of interest. Aleksandra Polkowska-Kramek, Robin Bruyndonckx, Thao Mai Phuong Tran, Worku Biyadgie Ewnetu, Maribel Casas, Juan Luis Ramirez Agudelo are employees of P95 Epidemiology & Pharmacovigilance, which received funding from Pfizer to conduct the research described in this manuscript and for manuscript development. Elizabeth Begier, Caihua Liang, Caroline Beese, Gordon Brestrich, Charles Nuttens, Lea Johanna Bayer, Bennet Huebbe, Bradford D. Gessner, Christof von Eiff are Pfizer employees and may own Pfizer stock. Gernot Rohde is an expert in the field of RSV and received an honorarium from Pfizer for input on the study design.

Ethical approval. This study used aggregated and anonymized data, therefore not requiring approval from Institutional Review Boards or Ethical Committees or informed consents from patients. The study was conducted in accordance with legal and regulatory requirements and research practices described in the Good Epidemiological Practice guidelines issued by the International Epidemiological Association.

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