Estimation of respiratory syncytial virus-associated hospital admissions in five European countries: a modelling study

Caroline Klint Johannesen,[a,b,**] David Gideonse,[c] Richard Osei-Yeboah,[d] Toni Lehtonen,[e] Ombeline Jollivet,[f] Rachel A. Cohen,[g] Arantxa Urchueguía-Fornes,[h,i] María Herrero-Silvestre,[h] Mónica López-Lacort,[h,i] Rolf Kramer,[f] Thea K. Fischer,[a,b,l] Terho Heikkinen,[j] Harish Nair,[d] Harry Campbell,[d] and Michiel van Boven,[c,k,*] for the PROMISE investigators[m]

[a]Department of Virus and Microbiological Special Diagnostics, Statens Serum Institut, Copenhagen, Denmark
[b]Department of Clinical Research, North Zealand University Hospital, Capital Region, Denmark
[c]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, the Netherlands
[d]Centre for Global Health, Usher Institute, The University of Edinburgh, Edinburgh, United Kingdom
[e]Department of Health Security, Finnish Institute for Health and Welfare, Helsinki, Finland
[f]Sanofi, Lyon, France
[g]GSK, Rockville, MD, United States
[h]Vaccine Research Department, Foundation for the Promotion of Health and Biomedical Research in the Valencian Region (FISABIO), Valencia, Spain
[i]CIBER de Epidemiología y Salud Pública, Instituto de Salud Carlos III, Spain
[j]Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland
[k]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[l]Department of Public Health, University of Copenhagen, Denmark

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Summary

Background Respiratory syncytial virus (RSV) can cause severe disease, notably among infants, older adults, and individuals with comorbidities. Non-systematic testing and differences in coding practices affect direct measures of the hospital disease burden. We aim to tackle this issue and estimate RSV-associated respiratory hospital admissions through time series modelling of hospital admissions.

Methods The number of RSV hospital admissions in Denmark, England, Finland, the Netherlands, and Spain were estimated with attribution analyses, using age-specific respiratory tract infection (RTI) admissions combined with virological data, both from routinely collected healthcare data. Analyses covered the years 2016–2023.

Findings The attributed incidence of RSV per 100,000 children 0–2 months ranged from 1715 in Denmark to 3842 in England. In older adults, substantial differences in the incidence of ICD-10 coded RSV hospitalisations were found, while the attributed RSV incidence was more comparable, ranging from approximately 100 per 100,000 in adults 65–74 years to 200 per 100,000 persons 75–84 years and 500 per 100,000 persons 85 years and older.

Interpretation RSV-attributed time series exhibit a high degree of synchronicity between participating countries, suggesting that this method for attribution addresses the known issues with underdiagnosis and misclassification. In the older age groups, a substantial proportion of RTI hospitalisations is attributed to RSV, underscoring the relevance of RSV as a cause of severe respiratory infections.

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Keywords: RSV; Respiratory tract infection; Hospital admissions; National register-based study; Time series analysis; Burden of disease

*Corresponding author. Centre for Infectious Disease Control, National Institute for Public Health and the Environment, the Netherlands.
**Corresponding author. Department of Virus and Microbiological Special Diagnostics, Statens Serum Institut, Copenhagen, Denmark.
E-mail addresses: r.m.vanboven-2@umcutrecht.nl (M. van Boven), caroline.klint.johannesen@regionh.dk (C.K. Johannesen).
[m]The members of PROMISE investigators are listed in the Acknowledgements section.

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) causes significant morbidity in children worldwide. Although well-established in children RSV is increasingly recognised as a cause of severe disease in older adults. Recent studies have focused on analysing this burden of disease but often face challenges such as selection bias or reliance on observational designs, which can lead to misdiagnosis due to testing issues and underreporting, especially in older adults. We searched PubMed with the NIH using the search terms [RSV burden], [Respiratory syncytial virus model], [RSV burden adults model], and [RSV model], including studies published at any date until December 31. 2023. We excluded studies that did not use statistical modelling to estimate the burden of RSV or were related to vaccine effectiveness or vaccine efficacy. The selected literature generally used time-series approaches. The studies typically found additional RSV-associated disease burdens in single populations and did not include the pandemic period. So, while previous research has provided reliable estimates by addressing these issues, studies have yet to examine the disease burden across multiple countries during both the SARS-CoV-2 pandemic and pre-pandemic periods. Meanwhile, new preventive measures have been developed to protect children and adults from infection and severe disease. Many countries are currently considering introducing RSV vaccines into public vaccination campaigns. Therefore, updated estimates of the age- and country-specific incidence of severe RSV disease are crucial for reliable foundations for public health policies.

Added value of this study

This study addresses misclassification and underreporting using a time series modelling method with national respiratory tract infection (RTI) hospital admission data, along with virus circulation indicators, in five European countries: Denmark, England, Finland, the Netherlands, and Spain. In adults aged 65 years and older, RSV-coded hospital admissions are rare, albeit increasing documentation supports that a non-negligible proportion of RTI hospital admissions is attributed to RSV. With this study, we assess that the proportion of RTI hospital admissions attributed to RSV in adults aged above 85 ranges between 5 and 12%, and that the correction of underreporting is between 3 and 49-fold in the same age group. Notably, the estimated incidence of RSV-related hospital admissions in older adults is consistent across countries, with rates of approximately 100 per 100,000 per year in adults aged 65–74 years, 200 per 100,000 per year in those aged 75–84 years, and 500 per 100,000 per year in persons aged 85 years and older.

Implications of all the available evidence

With the advent of vaccines and a new generation of monoclonal antibodies, accurate and reliable RSV disease burden estimates are crucial for evaluating the epidemiological landscape and assessing and monitoring the impact of interventions. Our estimates offer an important contribution to this evidence base, and our analytical methods offer a robust framework for future assessments of vaccine efficacy.

Introduction

Respiratory syncytial virus (RSV) is one of the leading causes of severe respiratory infections in children <2 years and has been the focus of preventive monoclonals and vaccine development over the past decade.[1] This has resulted in breakthroughs such that several prophylaxes have recently been authorised and used in high-income geographies.[2]

RSV is transmitted directly or indirectly through respiratory secretions and shows a strong seasonal pattern in temperate and subtropical climate zones.[3] RSV can cause severe respiratory disease, and acute infections can result in bronchiolitis or pneumonia, and hypoxaemia. In the most severe cases, patients are at risk of death from asphyxiation. Severe cases are most often reported among the very young (<1 year) and in the older population (≥65 years), and the burden of RSV disease in children has been a focus of investigation worldwide.[4]

In recent years, awareness has increased on the risk of severe RSV infection in older adults and adults with specific comorbidities.[5] Vaccines targeting this population have been introduced in several European countries, highlighting the need for reliable measurements for future effectiveness studies. The burden of disease data, however, is sparse in these populations, and underreporting is common. This is likely caused by limited awareness of RSV among health care practitioners, uncertainties with regard to testing practices, unreliability of diagnostic tests in older adults, and differences in the use of diagnostic codes to report and summarise the infections in the burden of disease studies.[6–8] In children, issues with underestimating the burden of RSV infections mostly arise from differences in registration and use of diagnostic codes.[9]

Here we propose a time series-based method to attribute the broad category of hospital admissions with respiratory tract infections (RTIs) to RSV, using the time-dependent number of positive virological isolates of respiratory pathogens as covariates. This serves to apportion the contribution of main respiratory pathogens such as influenza A and B, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and RSV to RTI admissions, thereby correcting for the underreporting of

RSV, especially in older age groups. This method has been employed for influenza and RSV[10–13] using data up to and including 2017. Here we report updated estimates for recent data that include the SARS-CoV-2 pandemic.

Methods

Data collection

We used national hospital registries containing individual-level patient data on all hospital admissions for Denmark, England, Finland, and the Netherlands, and we used a regional prospective hospital-based surveillance network for the Valencia area, Spain. From these data sources, described in detail earlier,[14] we aggregated age-specific weekly numbers of hospital admissions with the outcome of interest, i.e., all respiratory infections. The study period covers 2016 to 2023, with country-specific differences described below. The outcome of interest was defined using ICD-10 codes, except in Valencia, where case selection was based on influenza-like illness (ILI) criteria and PCR testing (see the section on country-specific details). The ICD-10 codes were selected to cover all acute respiratory tract infections (ICD-10: J00, J02–06, J09–18, J20–22, J40, U07.1, U07.2, U08-10) and RSV-coded hospitalisations were identified when any RSV code was related to the admission (RSV codes ICD-10: J12.1, J20.5, J21.0, B97.4). Hospital admissions were defined as any hospitalisation lasting more than 12 h. Scheduled or routine admissions were excluded. Using the country-specific sources of virological data, predominantly from tests conducted at hospitals and emergency clinics, aggregated non-age-specific weekly numbers of positive tests were generated and used as time-dependent covariates. Hospitalisations were divided based on age at admission into analytic groups: 0–2 months, 3–5 months, 6–11 months, 1–2 years (12–35 months), 3–4 years (36–59 months), 5–17 years, 18–64 years, 65–74 years, 75–84 years, and 85+ years.

Country-specific details

Denmark, 1. Jan 2017–30. Jun 2022

Weekly RTI infections were aggregated from individual contacts in the Danish National Patient Registry (NPR) which covers the full Danish population.[15] Infections that lasted longer than one week were counted only for the first week of hospitalisation. Weekly positive tests of RSV, SARS-CoV-2, and Influenza (collated from types A/B) were aggregated from the national microbiological database (MiBa)[16] where tests were predominately performed using real-time polymerase chain reaction (RT-PCR).

England, 8. Oct 2018–10. Apr 2023

Weekly hospital admissions with RTI were provided by the Hospital Episode Statistics (HES) database that monitors >98% of England's population.[17] Weekly positivity rates for RSV, SARS-CoV-2, and influenza, as well as the number of cases for influenza A and influenza B were provided by the United Kingdom Health Security Agency, based on the DataMart surveillance system and outcomes publicly published in the weekly reports[18] with 17 laboratories contributing data at present through weekly automatic electronic outputs. Participating laboratories test swabs for respiratory viruses using RT-PCR, although not all laboratories test for or report all viruses. The positivity rate for influenza A and influenza B was computed from these raw sources.

Finland, 1. Oct 2017–1. Mar 2023

The Finnish weekly RTI hospitalisations were based on the Finnish Care Register for Health Care (HILMO). HILMO covers individual-level clinical and administrative data from inpatient care, specialised outpatient care, and day surgeries. The weekly pathogen data was obtained through the National Infectious Diseases Register (NIDR). The NIDR captures records of selected microbiological findings and related diagnoses that all laboratories and physicians are obliged to report under the Communicable Disease Act. All positive test results for RSV, Influenza A, Influenza B, and SARS-CoV-2 are included in the register.

The Netherlands, 1. Jan 2013–1. Jan 2022

Weekly age-stratified hospital admissions with RTI and coded RSV were obtained from the Dutch Hospital Data (DHD) covering 2013–2021. These data cover over 99% of hospital admissions in the Netherlands. The DHD registry collects, manages, and processes hospital data and manages standards for its registration. Weekly age-aggregated virological data from 20 hospitals and peripheral diagnostic laboratories spread throughout the Netherlands were obtained for RSV, influenza A and B, and SARS-CoV-2 from the Dutch Working Group for Clinical Virology (NWKV). For a small number of cells containing values between 1 and 4 cases, these were reported as "1–4" for privacy reasons. For these cells, we imputed numbers between 1 and 4 uniformly at random.

Spain (Valencia), 10. Nov 2015–15. Oct 2023

In Spain–Valencia, all hospital admissions via Emergency Room that met preliminary inclusion criteria and were compatible with the ECDC-ILI case definition[19] were included. The data were collected as part of an active prospective hospital-based surveillance network (~1 million catchment population, 21% of the total Valencia population) organised through the Valencia Hospital Surveillance Network (VAHNSI) and coordinated by the Vaccine Research Department of FISABIO-Public Health. Patients ≥5 years old were included if, upon admission, they met symptoms compatible with ILI, defined as the presence of at least one respiratory symptom (cough, sore throat, or shortness of breath)

and at least one systemic symptom (headache, fever or feverishness, malaise, myalgia or general discomfort) with an onset of symptoms within 7 days prior to admission. In patients under 5 years, no specific symptomatology was required but respiratory symptoms had to have appeared no more than 7 days before hospitalisation. All included ILI patients (n = 13,028) were systematically tested for RSV and Influenza A and B via a multiplex-PCR. As the active surveillance was not conducted throughout the whole year, an imputation for the missing weeks (58 weeks in total) was used to get full time series, which is required to run the analysis. We imputed data for these weeks and for each age group using the seasonally decomposed missing value imputation from the imputTS package in R,[20] with more information in the Supplementary Material.

Time series analysis

Attribution of observed hospitalised RTIs to RSV was performed using Poisson regression in a Generalised Additive Model (GAM) framework with an interruption at the start of the pandemic period (week 9, 2020). In these analyses, the number of RTIs in each country and age group was explained by the background rate at which RTIs are generated, and by main circulating respiratory pathogens influenza A and B, RSV, and SARS-CoV-2 during the pandemic period. Specifically, the background rate was modelled using penalised splines, and covariates included the numbers of positives for the respiratory pathogens in virological surveillance data of each country (in England, the positivity rates were used as covariates). In addition, we allowed lags or leaps of the time series of the respiratory pathogen positives relative to the RTI case data to account for the fact that epidemic curves in different age groups may be shifted relative to each other and relative to the virological data.[13] Specifically, if we denote the set of pathogens considered as covariates by $P = \{RSV, influenza\ A, influenza\ B, SARS\text{-}CoV\text{-}2\}$, the expected number of cases in age group a at time t, $E(Y_{a,t})$, is given by

$$E(Y_{a,t}) = exp\left(s_a(t) + \sum_{i \in P} \beta_{i,a}\, N_{i,t-t_i}\right)$$

where $s_a(t)$ represents the penalised spline function in age group a, $t_i \in \{-3, -2, ..., 2, 3\}$ denotes the shift in weeks for pathogen i, and $\beta_{i,a}$ are the pathogen- and age-specific regression coefficients. As the observed cases $y_{a,t}$ are assumed to be Poisson distributed, we have

$$y_{a,t} \sim Poisson\left(E(Y_{a,t})\right)$$

Throughout, we employed second-order spline penalisation, and the number of knots was allowed to vary between 10 and 50, depending on the length of the time series and the data structure. Fitting of the regression models was performed using restricted maximum likelihood (REML), and for each country, age group, and period (pre-pandemic versus pandemic) selection of the optimal shifts was based on minimization of the Akaike Information Criterion (AIC), and selection towards plausible models with non-negative coefficients. It is worth noting that if all four pathogens were included this implies a comparison of $7^4 = 2401$ models. Not all countries could include all pathogens; however, for analysis restricted to the pre-pandemic period, SARS-CoV-2 was not included, yielding a maximum of $7^3 = 343$ models. R-code using the package 'mgcv'[21] was shared between countries. For each country, age group, and period (pandemic versus pre-pandemic) attribution of RTI cases to RSV was based on the best fitting models. Specifically, RSV attribution was based on the difference between the expected number of RTI cases in the full best fitting model with the best fitting model when the number of RSV virological positives was set to zero. Where models attributed a negative proportion of admissions to RSV, we report RSV to attribute no admissions (0) as negative attribution is biologically implausible. This occurred in six models, namely age groups 3–4 years, 5–17 years in Finland and Spain, and in 18–64 years in Finland.

Calculation of outcomes

We used time series analysis to estimate RSV-attributed hospital admissions specific to age groups and countries, resulting in attributed admissions by weeks included in the model. The yearly average of RSV-attributed hospital admissions was determined by using the estimated RSV attribution for each week in both the age-group and country-specific models. We aggregated these weekly figures to get a total, which we then divided by the total duration of data collection in years.

For RSV-coded hospital admissions, we used the actual number of registered RSV admissions from the databases and divided this by the total time of data collection in years. To find the attributed admissions per RTI-coded admission, we calculated the total number of RSV-attributed admissions and divided that by the total number of RTI admissions within the specific age group and country.

Next, we determined the incidence of RSV-attributed admissions (per 100,000 persons) by dividing the number of RSV-attributed admissions during the studied period by the population at risk during that same period. Finally, we calculated the attribution ratio for RSV-coded admissions by dividing the total number of RSV-attributed admissions by the total number of RSV-coded admissions in the specific age group and country following the form RSV-attributed/RSV-coded (and Spain RSV-attributed/RSV-confirmed). A ratio above 1 indicates that there may be underreporting and/or underdiagnosis of RSV within that age group.

Role of the funding source
The funding source organised the collaboration and received a final report on the project. The funding source had no influence on the scientific content of the project.

Results

RSV-attributed RTI admissions
Through the age group- and country-specific time series analysis, we estimated the number of RTI admissions that could be attributed to RSV. Absolute numbers vary substantially between countries because of differences in population size. Overall, the distribution of RSV-attributed admissions followed a U-shaped pattern across age groups, with higher numbers observed among young children (<5 years) and older adults (≥65 years) (Table 1; see Supplementary Table S1 for detailed results).

The incidence of RSV-attributable hospitalisations per 100,000 person-years was calculated for each age group to account for differences in population size across countries. In all countries, the incidence rates follow a clear trend. The youngest age groups have the highest incidences (e.g., 0–2 months: 2280 in the Netherlands, 2200 in Valencia, 3843 in England). In age groups 3–4 years and 5–17 years, the incidences fall to under 50 per 100,000 in all countries where it was possible to estimate the RSV-attributed admissions (with the exception of England in the age group 3–4 years). In older adults the attributed yearly incidence per 100,000 was comparable across countries, ranging from approximately 100 in adults 65–74 years (Denmark: 126; England: 70; Finland: 53; the Netherlands: 87; Spain: 38), approximately 200 in persons 75–84 years (Denmark: 210; England: 221; Finland: 160; the Netherlands: 220; Spain: 140), and approximately 500 in persons 85 years and older (Denmark: 590; England: 587; Finland: 490; the Netherlands: 480; Spain: 270), with Spain reporting the lowest incidences in all three older adults age groups (Table 1). Again, the distribution of RSV-attributed admissions was U-shaped for incidence across age groups, with higher incidences among young children (<5 years) and older adults (≥65 years).

RSV-coded and RSV laboratory-confirmed hospital admissions
Fig. 1 presents the weekly incidence of RSV-coded hospital admissions by main diagnosis. The figure shows similar seasonal patterns in participating countries. Spain (Valencia) was not included, as RSV-coded admissions were not available for this country due to an insufficient sample size. However, substantial differences in incidences were seen, particularly in adult age groups, with the Finnish incidence of RSV-coded hospital admissions being the highest and the Danish the lowest.

The yearly average numbers of RSV-coded hospital admissions shown in Table 1 followed this pattern, with the highest average number of admissions in the youngest children (0–2 months of age), and the lowest number in the oldest children: 3–4 years and 5–17 years (Supplementary Table S1). An increase with age in the number of RSV-coded admissions was observed across all countries from the 65–74 years age group onwards, though the numbers were relatively lower in Denmark and Spain (Table 1).

RTI-coded hospital admissions
The weekly number of RTI-coded hospital admissions was used as the outcome in the model. As expected, these number differ substantially between age groups and countries. Weekly numbers are shown by the grey dots in Figs. 2–6. Clear patterns of seasonal variation were observed in the age-specific RTI-coded hospital admissions, with yearly winterly peaks on both sides of the pandemic period 2020–2022. With rising age, the number of "out-of-season" RTI-coded hospitalisations rose in all participating countries. The predicted numbers of RTI-coded hospital admissions in Denmark, Finland, the Netherlands, and Spain (Figs. 2, 4–6 (grey lines)) followed the observed closely in the youngest age groups and the elderly age groups (0–2 months, 3–5 months, 6–11 months; and 65–74 years, 75–84 years, and 85+ years, respectively). In England, the observed fit was similar between all age groups.

Ratio of attributed to coded RSV admissions
The attribution ratio addresses underreporting, underdiagnosis and/or misclassification in the specific age groups and country. When ratios are below 1 (for children <3 years in Finland and Spain, and 0–2 months in Denmark and the Netherlands), the time series analysis attributed fewer admissions to RSV than recorded in the medical records. With ratios above 1, for example, in children in the Netherlands aged 3–5 months (ratio: 1.2), the yearly average number of attributed RSV admissions was higher than the yearly average number of RSV-coded admissions. The ratios of RSV-attributed admissions to RSV-coded admissions were above one in all age groups above 3 years (Table 1). The ratios increased generally with age and the highest ratios were found in the older Danish adults, ranging from 29 (29 RSV admissions attributed per 1 RSV-coded admission) (18–64 years) to 49 in 85+ years. In comparison to these extremes, the 85+ ratios were 18, 2.9, and 7.6 in England, Finland, and The Netherlands respectively (Table 1).

In Valencia (Spain), the RSV-coded admissions were substituted by RSV laboratory-confirmed admissions. The ratio of attributed RSV admissions to RSV laboratory-confirmed admissions in Valencia ranged from 0.41 (3–5 months of age) to 4.8 (18–64 years) (Table 1).

Countries using nationwide databases & RTI admissions

Country	Age group	RSV-attributed hospital admissions (yearly average)	RSV-coded hospital admissions (yearly average)	Attributed per RTI-coded admission	Incidence of RSV-attributed admissions (per 100,000 per year)	Ratio of attributed to coded RSV admissions
Denmark	0–2 m	266	301	0.37	1715	0.88
	3–5 m	298	276	0.33	1927	1.1
	6–11 m	230	132	0.19	742	1.7
	1–2 y	380	180	0.12	310	2.1
	65–74 y	806	21	0.09	126	38
	75–84 y	961	29	0.08	253	33
	85+ y	730	15	0.08	588	49
England	0–2 m	5876	4884	0.25	3842	1.2
	3–5 m	3727	2377	0.23	2437	1.6
	6–11 m	5142	2527	0.18	1681	2.0
	1–2 y	10,113	3509	0.16	785	2.9
	65–74 y	3873	899	0.03	70	4.3
	75–84 y	7452	1165	0.04	221	6.4
	85+ y	8087	996	0.05	587	8.1
Finland	0–2 m	268	588	0.19	2124	0.46
	3–5 m	146	271	0.24	1154	0.54
	6–11 m	76	176	0.09	302	0.43
	1–2 y	255	259	0.09	234	0.98
	65–74 y	357	186	0.03	53	1.9
	75–84 y	581	242	0.04	162	2.4
	85+ y	711	247	0.05	489	2.9
Netherlands	0–2 m	978	1055	0.27	2280	0.93
	3–5 m	496	415	0.26	1156	1.2
	6–11 m	633	322	0.22	737	2.0
	1–2 y	906	259	0.16	258	3.5
	65–74 y	1545	257	0.08	87	6.0
	75–84 y	2122	280	0.09	222	7.6
	85+ y	1702	156	0.12	483	11

Countries using local screening of medical records & ILI case definition

Country	Age group	RSV-attributed hospital admissions (yearly average)	RSV-coded hospital admissions (yearly average)	Attributed per ILI-admission	Incidence of RSV-attributed admissions (per 100,000 per year)	Ratio of attributed to coded RSV admissions
Spain[a]	0–2 m	50	75	0.26	2200	0.66
	3–5 m	28	41	0.28	1244	0.69
	6–11 m	11	27	0.14	249	0.41
	1–2 y	35	38	0.17	180	0.93
	65–74 y	40	19	0.07	38	2.1
	75–84 y	91	35	0.11	135	2.6
	85+ y	79	29	0.12	268	2.7

Full results, including age groups 3–4 years, 5–17 years, and 18–64 years are presented in Supplementary Table S1. [a]For Spain (Valencia) RSV laboratory-confirmed hospital admissions are used as an indicator of virus circulation, and ILI diagnosed admissions are used as a proxy for RTI-coded admissions.

Table 1: **Summary of results per country and age group.**

RSV-attributed hospitalisations during the pandemic

In all the participating countries, except Valencia and the Netherlands, where the data collection ended in the early phase of the SARS-CoV-2 pandemic, the RSV-attributable admissions to hospitals were close to 0 in the first year of the pandemic, from March 2020 to March 2021 (Figs. 2–6). In the second year of the pandemic, RTI hospital admissions were again attributed to RSV from the middle of 2021 in all countries but not in all age groups. In the Netherlands, there were no RSV-attributable cases in age groups 3–4 years, 5–17

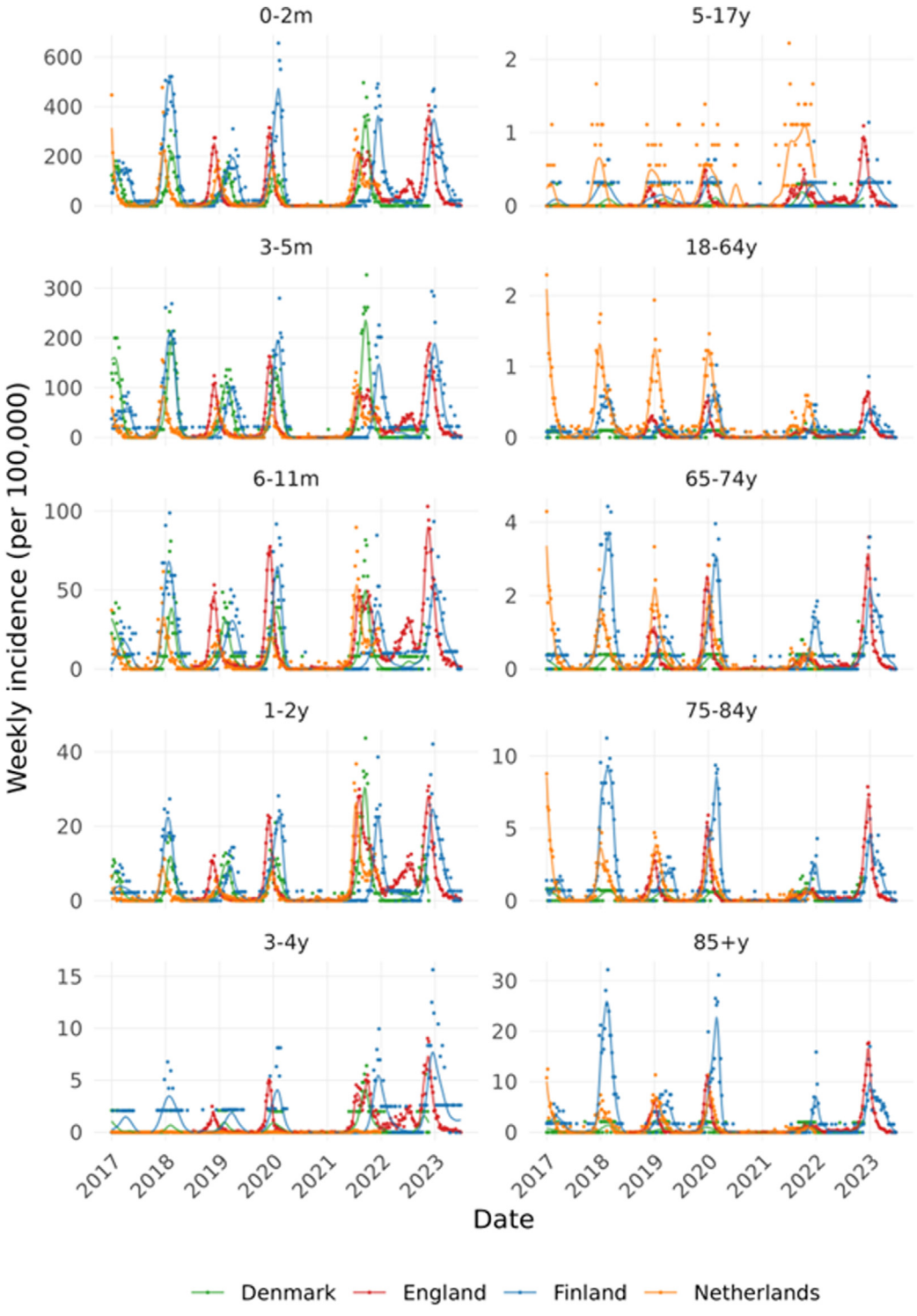

Fig. 1: Weekly incidence of RSV-coded hospital admissions in four European countries using main diagnoses over the period 2017–2023. Notice that the period covered differs between countries. Also note the range differences on the y-axes. Dots represent the data and lines represent the trend (fitted to the log (1+ incidence) transformed data using cubic splines).

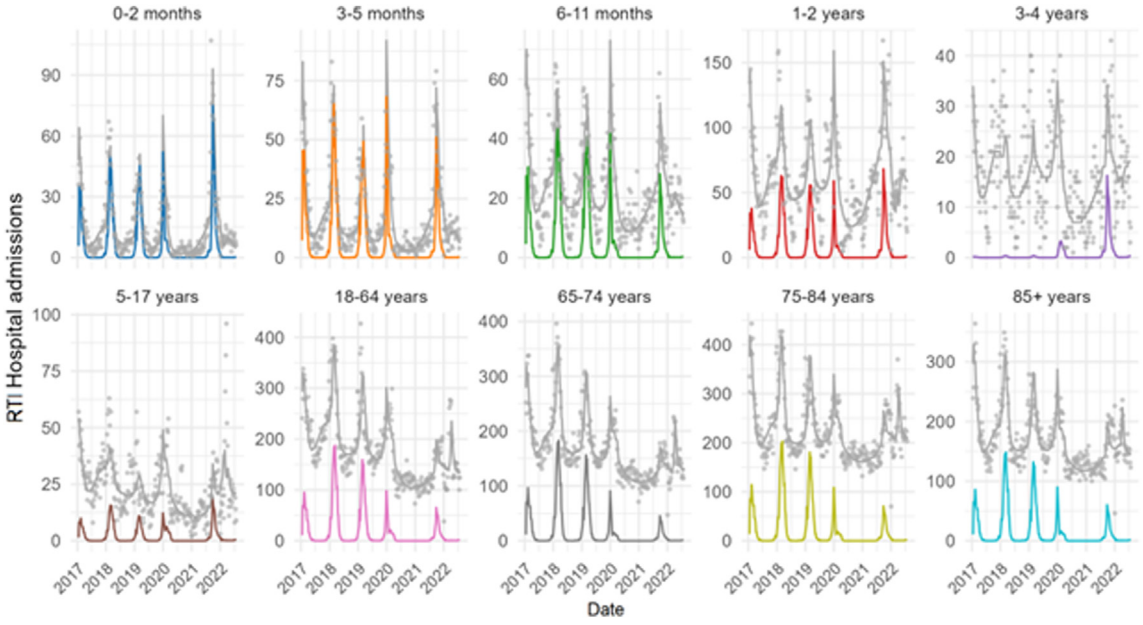

Fig. 2: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV laboratory-confirmed in Denmark (2017–2022, 6 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

years, and 18–64 years (Fig. 5). The pre-pandemic pattern of epidemic peaks followed by periods of few to no admissions was re-established after 2021 in Denmark, Finland, and to some extent in the Netherlands and England. In the Netherlands, our RSV attributions show a twin-peaked season in 2021–2022 for age groups 0–2 months, 3–5 months, 6–11 months, 1–2 years, 64–74 years, 75–84 years, and 85+ years. In England the RSV-attributable admissions took on another form after the pandemic, with one broad epidemic curve in 2021, followed by a double-peaked curve in 2022 (Fig. 3).

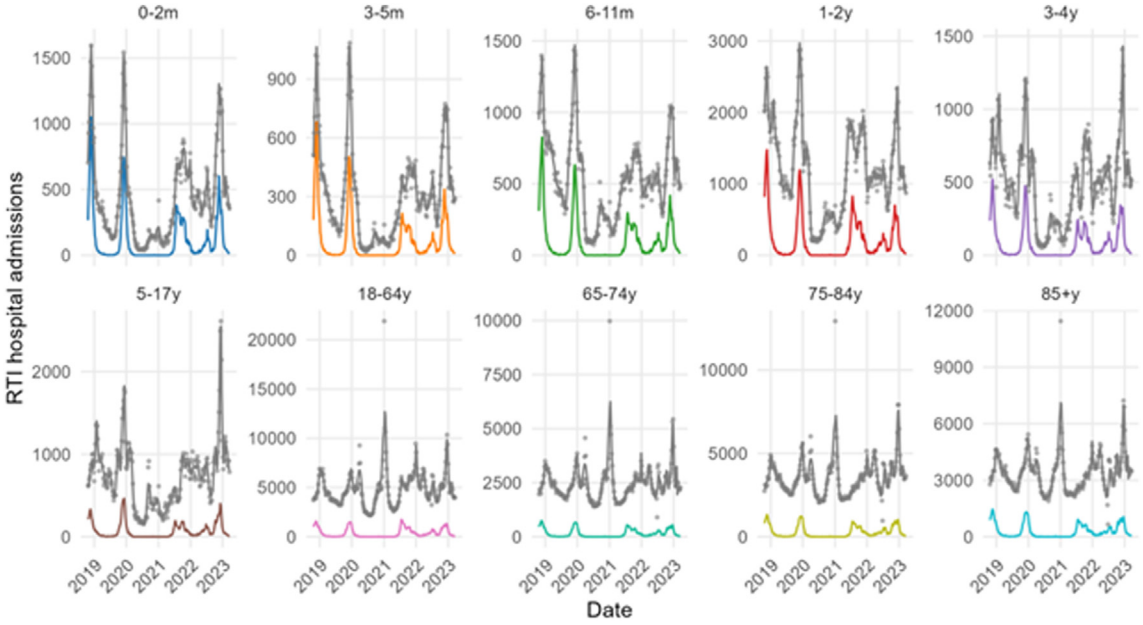

Fig. 3: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in England (2017–2023, 7 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

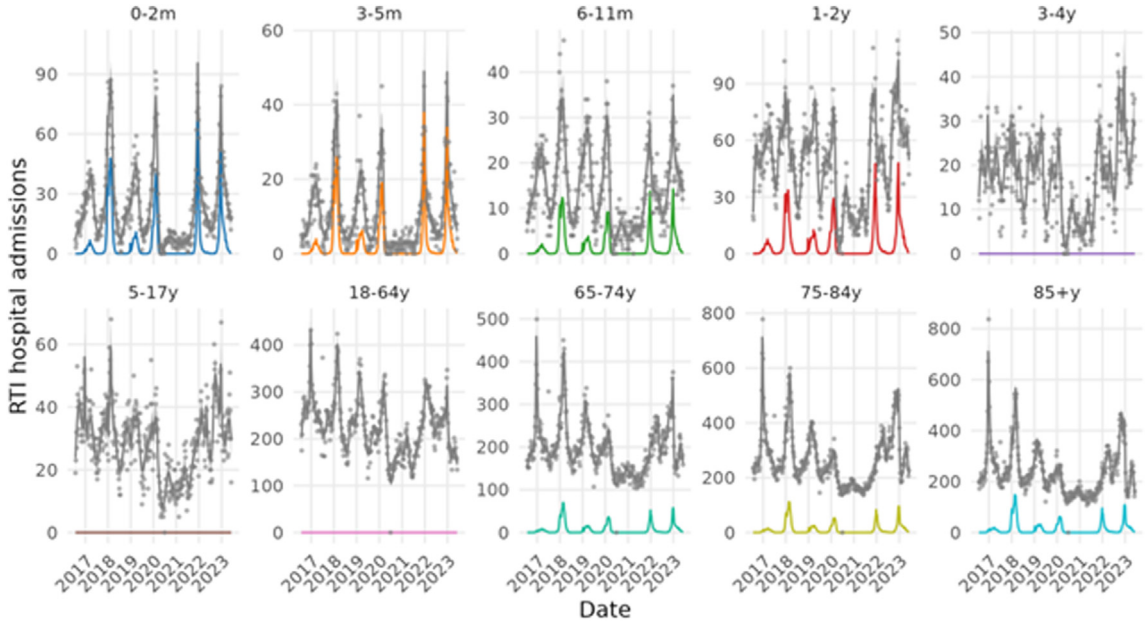

Fig. 4: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in Finland (2017–2023, 7 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

Discussion

Our analyses provide estimates of the age-specific rates of RSV-attributed hospital admissions in five European countries, spanning the full North–South axis and including both the pandemic and pre-pandemic periods. Rates of RTI hospital admissions attributed to RSV were expectedly highest in infants. However, RSV-attributed hospital admissions were also estimated in other age groups and increased with increasing age in older age groups (Table 1, Figs. 2–6). In older age groups, large

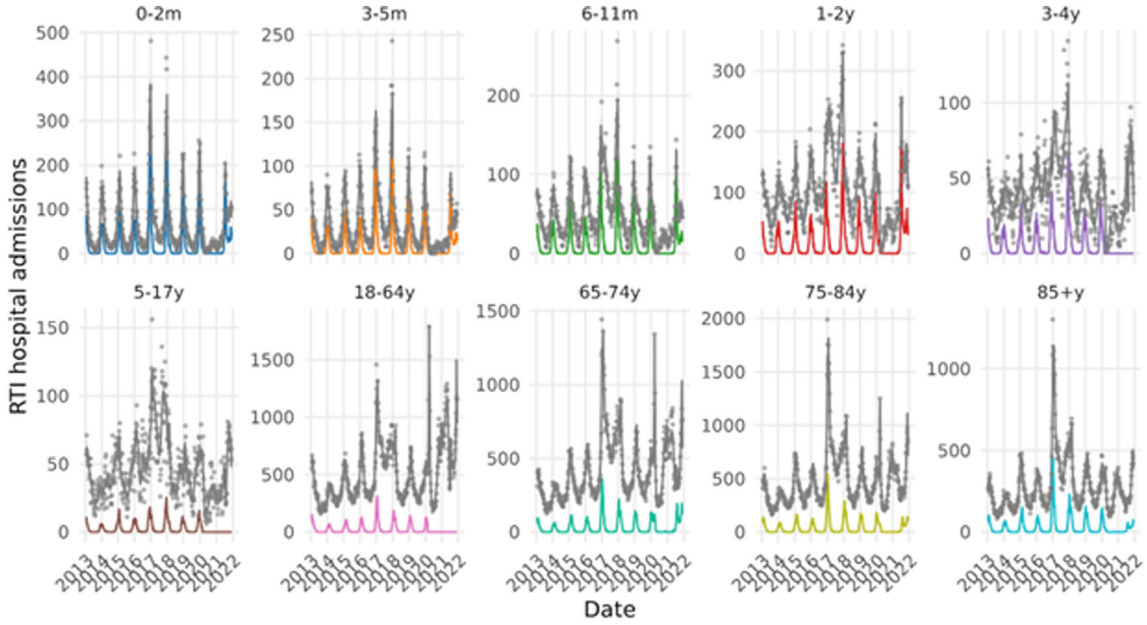

Fig. 5: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in the Netherlands (2013–2021, 9 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines).

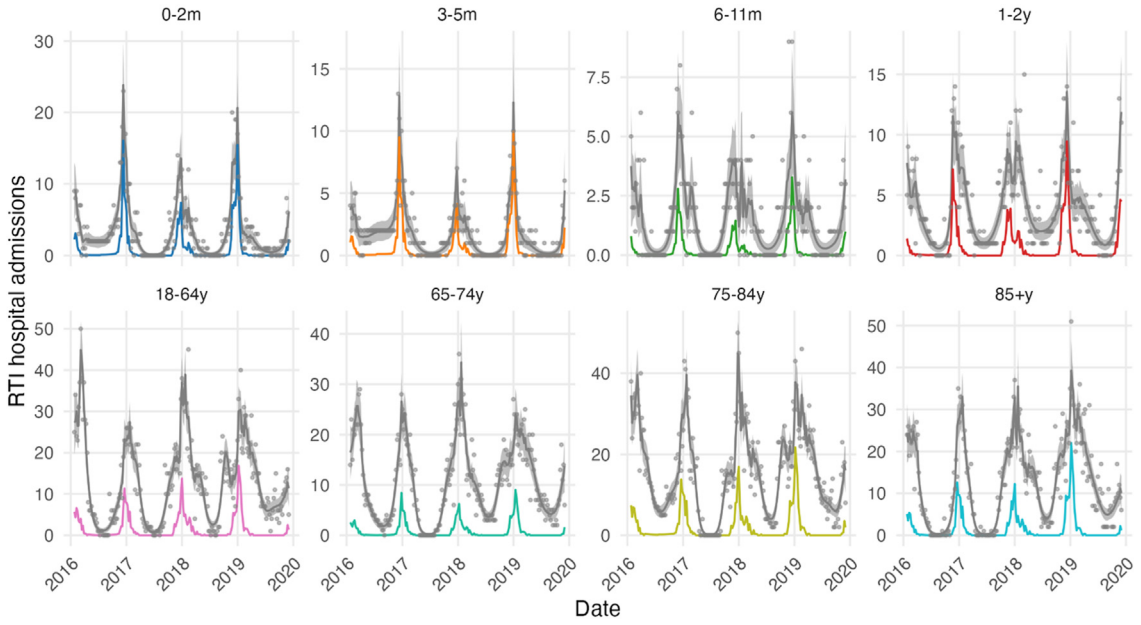

Fig. 6: Attribution of hospital admissions for respiratory tract infections (RTIs) to RSV in Spain (Valencia region) (2016–2019, 4 years). Shown are the total weekly number of RTI hospital admissions (grey dots), the fitted overall numbers of RTIs (grey lines, shaded bands represent 95% CIs), and RSV-attributed RTI admissions (coloured lines). Notice that RSV laboratory-confirmed hospital admissions are used as a proxy for RSV-coded hospital admissions and influenza-like illness (ILI) diagnosed admissions are used as a proxy for RTI-coded admissions.

differences are observed between the number of RSV-coded infections and RSV-attributed infections (Attributed ratio, Table 1), underlining the issue with underreporting of RSV in these age groups where the true hospital burden caused by RSV is difficult to ascertain.[22] Building on an earlier study,[13] our attribution analyses presented here have provided such estimates. Estimated RSV incidence was similar across countries in different age groups, ranging from roughly 100 per 100,000 in adults 65–74 years 200 per 100,000 in persons 75–84 years, and 500 per 100,000 in persons 85 years. Comparably, a recent meta-analysis of clinical studies describing the incidence of adult RSV before the COVID-19 pandemic found a hospitalisation incidence of 178 per 100,000 adults in 65+ years.[23] Our previous estimates of RSV-attributable RTI admissions in European countries were used to extrapolate the burden of RSV in all EU/EEA countries.[24,25] We propose to update that work on the basis of this study to provide country-specific estimates for the burden of RSV in European countries without comprehensive healthcare registration data or surveillance studies comparable to that of the Valencia region in Spain.

Our analyses show that a non-negligible proportion of RTI hospital admissions in persons 65 years and older can be attributed to RSV. A main strength of our analyses is that they have yielded estimates of the attributed incidence of RSV hospital admissions in five European countries using shared data collection protocols and methods of analysis. A further strength is that the analyses are based on routinely collected population-level data, with hospital databases covering the whole population in Denmark, England, Finland and the Netherlands, thereby minimising the possibility of inclusion bias affecting the results.

Throughout, attribution of RTI-coded admissions in European hospitals to RSV is based on time series analyses of country-specific RTI hospital admission data together with country-specific virological data of RSV, influenza A and B virus, and SARS-CoV-2, or other indicators of pathogen circulation. As RTI hospital admissions can be caused by various infections, we assumed a smoothly varying background rate at which RTIs are generated by pathogens not included in the virological data, modelled with penalised splines. In this manner, sudden peaks in RTI admissions that co-occur with peaks in virological positives can be attributed to the pathogens included as covariates. This could have caused both over- and under-attribution of RTI admissions to RSV. A main cause for over-attribution could be the widespread circulation of pathogens not included as covariates in the analyses that peaked at the same time in the year when the RSV epidemic peaked. These pathogens include human metapneumovirus, parainfluenza virus, rhinovirus, and others.[26] Usually, however, these other pathogens are quantitatively considered less important causes of medically attended RTI than influenza virus, RSV, and SARS-CoV-2,[27,28] and although these pathogens can sometimes cocirculate with RSV, co-circulation is not perfect and also does not

occur in every winter season.[29–31] Alternatively, under-attribution of RTI admissions to RSV could also be possible, for instance, because part of the RSV admissions is contained in the spline background. Additionally, throughout we assumed time-independent regression coefficients for pathogens included as covariates. If, for some reason, these would not be constant, for instance, by changing rates at which virological positives are reported, tested for, or by changing severity of infection caused by pathogen evolution,[32] there could have been some degree of under-attribution in some years and over-attribution in other years.

In an earlier study, we used a relatively parameter–sparse combination of harmonic functions (i.e., sines and cosines) to describe the background rates, a method with easier interpretation but a risk of over-attribution to covariates due to inflexible background rates.[13,33] Our current method of analysis using penalised splines does not suffer from this problem and offers a flexible alternative that makes less stringent assumptions. A full sensitivity analysis of all models and countries is outside the scope of the current study. Still, for the Netherlands, we did explore scenarios with a reduced number of knots in the spline background rates (25 instead of 50), with a more restrictive set of possible lags and leaps between hospital admissions and virological data (−2 to +2 weeks), and with results of second- and third-best models. We found that, generally, there can be sizeable absolute differences in the estimated yearly numbers of RSV-attributed admissions, but the absolute deviations are usually small, especially in younger age groups (<10%) (Data not shown).

To enable joint analysis, we allowed for slight differences in data collection between countries. In the case of the Valencia region (Spain), differences with other countries are larger, as these analyses are based on ILI inclusion criteria rather than RTI hospital admissions, and indicators of virus circulation are laboratory-confirmed RSV and influenza A infections of all included hospitalisations rather than (independent) virological test data with no specific denominators. Additionally, ILI surveillance is not performed during the summer period, and therefore, approximately 7% of the ILI cases have been imputed. Therefore, a comparison of analyses from Spain (Valencia) with other countries should be made with caution, as ILI hospital admissions are a subset of RTI hospital admissions and the attributions to RSV in the Spanish dataset likely represent an underestimation of the true number of RSV hospitalisations of the total RTI admissions. Nevertheless, the inclusion of data from Valencia allowed us to see the impact of using similar methods of analysis in settings with different data collection possibilities and methods of registration. As such, Spain (Valencia) may be the most relevant result for other countries/regions with surveillance data and not registering hospital admissions with ICD-10 codes, providing an opportunity to show the impact of RSV in already well-established influenza sentinel sites which often use ILI as the main case definition.

In young age groups (0–2 years) we observed an excellent agreement between the ILI-based inference and the subset of ILI cases that tested positive for RSV (Supplementary Material, Fig. S1). In older age groups, the attribution analyses correctly identified the epidemic peaks, but the number of attributed RSV cases was substantially higher than the number of RSV-positive cases. This may indicate low test sensitivity or lack of fit with RSV symptoms and the ILI case definition in these older age strata.[8] In summary, these analyses demonstrate a strong concordance between the attributed and test-positive RSV cases, providing additional confidence in the validity of our attribution methodology. We included as Supplementary material a figure of the observed RSV laboratory-confirmed data alongside the model-attributed RSV infections across the entire period. Overall, we found a good agreement between the model predictions and the observed data in children below 5.

Overall, our statistical approach to attribute RTI hospital admissions to RSV is flexible and readily produces estimates of the hospital burden of RSV in different age groups. We believe that future integrated analyses of the data presented here will aid in obtaining a more mechanistic understanding of the factors affecting the dynamics and burden of RSV in different age groups.[34] This will enable informed vaccination decisions that take both the direct and indirect effects of vaccination on the circulation and burden of RSV into account. In our analysis, the differences between countries are smaller for attributed RSV admissions based on RTI admissions than for coded RSV hospital admissions, especially in older age groups, revealing a comprehensive issue with underreporting of RSV. We believe that this calls for a closer investigation into the causes of RTI hospital admissions in older adults to uncover the true burden of disease caused by RSV. The finding of substantial, consistent estimates of RSV-attributable RTI hospital admissions is also of considerable interest, given the options for vaccination in older adults.

Contributors

OJ, AUF, CKJ, TM, DG, RAC, RK, TH, TKF, MVB, ROY, HC contributed to the design of the study. OJ, AUF, ML-L, MHS, CKJ, TM, MVB, RAC, ROY contributed to the data extraction for this work and to the analysis of the data. CJK and MVB contributed to the data visualization and manuscript writing. All authors reviewed and validated this manuscript.

Data sharing statement

This study is based on routinely collected health care data that the authors are not available to share. Please refer to the country-specific data description in the supplements for details on data sources and apply for data access with the data owners. The authors can share the study protocol upon request.

Declaration of interests

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PROMISE investigators: Harish Nair (University of Edinburgh), Hanna Nohynek (THL), Anne Teirlinck (RIVM), Louis Bont (University Medical Center Utrecht), Peter Openshaw (Imperial College London), Andrew Pollard (University of Oxford), Veena Kumar (Novavax), Elizabeth Begier (Pfizer), Jim Janimak (GlaxoSmithKline), Jenny Hendrix (Janssen), Rolf Kramer (Sanofi), Alejandro Orrico Sánchez (FISABIO), Eva Molero (Teamit).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101227.

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