Respiratory syncytial virus-attributable hospitalizations among adults in high- and middle-income countries: application of the Global Burden of Disease framework

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Summary

Background Respiratory syncytial virus (RSV) in adults is typically underdiagnosed due to non-specific symptoms, infrequent routine testing, and low-test sensitivity; consequently, its impact is not well understood. To address this gap, we developed a novel approach to estimate adult RSV-related hospitalizations, leveraging methods from the Global Burden of Disease (GBD) study.

Methods We collected aggregated clinical data from hospital statistics and insurance claims on respiratory and cardiorespiratory hospitalizations and RSV activity proxies for age groups 18–59 years, 60–74 years, ≥60 years, and ≥75 years in 15 countries (Argentina, Brazil, Canada, Chile, Georgia, Germany, Greece, Ireland, Italy, Japan, Mexico, New Zealand, Poland, Spain, and the United States) between 1992 and 2021. In addition, we collected RSV surveillance data, i.e., the percentage of samples tested positive for RSV from the WHO GISRS platform—the Global Influenza Surveillance and Response System and from country-specific reporting platforms for countries from North and South America, Europe and Asia, covering the years 2015–2023. Using the GBD comparative risk assessment framework, we estimated exposure-response relationships between RSV activity and hospitalizations using generalized additive models (GAMs), adjusting for trend, seasonality, meteorological influence and influenza activity, between the years 2015–2019, and calculated the population attributable fraction (PAF) and RSV-attributable hospitalizations. We evaluated the predictive power of surveillance-based versus hospital-based RSV proxies based on adjusted R^2, and generalized cross-validation (GCV) score.

Findings We identified significant relationships (p-value < 0.01) between RSV activity and increased respiratory and cardiorespiratory hospitalizations among adults. Generally, hospital-based RSV proxies predicted hospitalization better than surveillance-based proxies. RSV-attributable hospitalization rates and PAFs varied substantially by age and country. The highest annual RSV-attributable hospitalization rates were estimated for individuals 75 years and older, ranging from 110.9 (95% uncertainty interval [UI]: 66.9–156.1, median: 113.5, inter quartile range [IQR]: 10.4) per 100,000 population in Argentina for respiratory hospitalizations to 1199.8 (1087.0–1313.8, 1209.5, 88.9) per 100,000 in New Zealand for cardiorespiratory hospitalizations. The lowest RSV-attributable hospitalizations, for respiratory and cardiorespiratory diseases, were found for adults aged 18–59 years in Spain with 5.0 (95% UI: 0.8–9.3) hospitalizations per 100,000 for the hospital-based proxy.

Interpretation Innovations introduced by this analysis include non-parametric modelling of the exposure-response relationship between RSV activity and hospitalizations and evaluating the predictive reliability of two RSV proxies. Our findings highlight the substantial adult RSV disease burden, provide estimates for countries with no prior data (particularly those in (sub)tropical climates such as Mexico and Brazil), and illustrate the considerable geographic variability in adult RSV incidence. These results can guide future research, interventions, and policy decisions, including those involving adult RSV vaccines.

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Research in context

Evidence before this study

To date, few studies have rigorously evaluated the impact of respiratory syncytial virus (RSV) on adults with most existing research relying on outdated statistical methodologies, predominantly using parametric models that assume a linear exposure-response relationship between RSV and health outcomes and incorporate a sinusoidal seasonality pattern. Differences across studies in outcome measures applied, including the use of divergent proxy measures for RSV activity, as well as other methodological heterogeneity make it difficult to compare findings between studies. Moreover, most studies have been conducted in high-income countries with temperate climates, such as the United States and various European nations while middle-income countries in (sub)tropical climates and regions, such as Latin and South America and Asia, remain grossly underrepresented.

Added value of this study

This study offers the first comprehensive estimation of RSV-attributable hospitalizations in adults across 15 countries spanning five continents—North America, South America, Europe, Asia, and Oceania—providing estimates for countries and climates previously lacking data. Utilizing robust surveillance and clinical informatics data (i.e., electronic medical record and claims) from 2015 onwards coinciding with the initiation of the WHO surveillance system, this analysis applies a rigorous statistical approach that draws from comparative risk assessment (CRA) and other key methods from Global Burden of Diseases, Injuries and Risk Factors Study (GBD) to systematically quantify and compare disease burden attributable to selected risk factors. Additionally, this analysis compared the ability of surveillance-based versus hospital-based proxy data for RSV activity to predict hospitalizations to better inform decisions about the use of different RSV measures.

Implications of all the available evidence

RSV poses a significant risk for respiratory and cardiorespiratory disease occurrence and exacerbation, leading to increased hospitalizations during periods of heightened viral activity. This innovative methodological framework allows for more accurate estimates of the true burden of RSV in adults on both respiratory and cardiorespiratory diseases in 15 countries, offering substantial improvements over prior studies. Importantly, our findings underscore the high number of potentially preventable hospitalizations of adults due to RSV, particularly in (sub)tropical regions, and can guide intervention strategies, including RSV vaccines for adults and lays the groundwork for development of a global model.

Introduction

Respiratory syncytial virus (RSV) is a well-recognized aetiologic agent of childhood respiratory infections.[1] However, the burden of RSV in adults and particularly those older than age 60 remains largely understudied, despite growing evidence of its clinical relevance.[2–4] A recent study by Li et al.[5] estimated 787,000 (95% confidence interval [CI]: 460,000–1,347,000) RSV-associated hospitalizations among older adults in high-income countries in 2019. RSV is commonly monitored through population-level systems like WHO's Global Influenza Surveillance and Response System (GISRS), but accurately assessing its health burden is challenging due to factors including the virus's ubiquity, non-specific symptoms, exclusion of some RSV cases by surveillance definitions (e.g., some definitions of influenza-like illness (ILI) require fever, which is uncommon in RSV), limited routine laboratory testing, and low testing sensitivity in adults.[6–10] Additionally, older adults often exhibit reduced viral presence, especially when tested late in the disease course, leading to false negatives.[8,11] Finally, although there is increasing evidence of RSV's contribution to exacerbations of cardiac disease (such as congestive heart failure) in older adults,[12,13] this relationship is even less well characterized than the association of RSV with lower respiratory infections. The role of adult RSV in fatal and non-fatal disease is vastly underestimated when analyses focus solely on diagnosed cases.[2,6,8,14,15] With the introduction of RSV vaccines, expanding our limited understanding of the true extent of RSV-induced health outcomes in adults becomes even more urgent.

In recent years, RSV surveillance systems have been implemented in various locations, spanning low- to high-income countries, to provide reliable data for accurate disease burden estimates across all age groups.[16] These surveillance data allow alternative approaches to estimating RSV-attributable burden through indirect statistical modelling strategies, similar to approaches

used for estimating influenza burden.[17–21] Commonly, time-series models, are employed to estimate baseline mortality using multi-year averages, with influenza-attributable burden defined as excess mortality above expected baseline.[18–20] Due to several limitations of this approach, including a failure to address potential confounders, recent studies have quantified attributable burden based on estimated exposure-response relationships between viral activity and increased incidence of health outcomes.[17,21] However, to date, few studies have used this modelling strategy to estimate RSV-related health outcomes.

In this study, we implemented a novel statistical approach designed to address key limitations of previous research. We estimated the incidence of RSV-related hospitalizations using the comparative risk assessment (CRA) framework, a fundamental component of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), employed to systematically estimate disease burden attributable to selected risk factors.[17,22] As part of the CRA, we modelled exposure-response relationships between community RSV activity and respiratory and cardiorespiratory hospitalizations, testing the predictive power of surveillance-based and hospital-based proxies for RSV activity. Using proxy data and exposure-response estimates, we calculated population attributable fractions (PAFs; the proportional reduction in hospitalizations that would occur if RSV exposure were reduced to zero) to estimate RSV-attributable hospitalizations across four adult age groups and 15 countries.

Methods

Study design

This is a population-based ecological modelling study using advanced statistical methods, such as non-parametric generalized additive models to capture potentially non-linear exposure-response relationships between RSV and hospitalizations. Estimated exposure-response relationships are then combined with exposure data to calculate PAFs. PAFs were then multiplied with overall respiratory and cardiorespiratory hospitalization data to derive RSV-attributable hospitalization estimates. Individual estimation steps are outlined in Fig. 1.

Data sources

RSV surveillance data and modelling

RSV surveillance data for 54 countries and one special administrative regions were gathered from the GISRS platform—the Global Influenza Surveillance and Response System maintained by WHO, which also collects RSV information[23] —as well as from country-specific reporting platforms. Additional meta-information on WHO and CDC RSV surveillance, detailing time periods, types of surveillance systems, and data sources for countries for which we provide estimations of RSV-attributable hospitalizations are provided in Table 1. Data reported included the number of samples and those testing positive for RSV and influenza, enabling calculation of the percentage of positive samples for either pathogen, referred to as RSV activity or influenza activity, respectively. To impute missing data and correct for implausible values, we generated a modelled time-series of RSV activity based on a time-space regression model developed by the Institute for Health Metrics and Evaluation (IHME), called RegMod.[24] RegMod allowed us to incorporate all available RSV surveillance data, weigh these data by sample size to capture measurement reliability, and incorporate key covariates such as seasonality and meteorology into our models. RSV activity was considered the outcome variable, while season, temperature, humidity, population density, and latitude served as predictor variables. To reflect clustering within geographical regions, and to borrow strength from neighbouring countries, we incorporated cascades for region. Models were run separately by hemisphere. We produced time series estimates from 2015 to 2023 for all locations that implemented RSV surveillance (Supplementary Table S2) and three additional countries that do not report RSV data at all (New Zealand, Italy, and Japan). We included all available RSV data to stabilize models and borrow strength across different locations. The global Mean Absolute Errors (MAE) were 0.060 for in-sample and out-of-sample predictions, while the Root Mean Square Error (RMSE) was 0.087. The similarity between in-sample and out-of-sample errors is an indicator of the stability and generalizability of the model. Model performance, as expressed through MAEs, varied across regions (Supplementary Table S3), and showed stark differences by countries (Supplementary Table S3). For the purpose of this study, we assessed the predictive power of modelled RSV data for the 15 countries included in our analysis. To enhance the stability and robustness of the predictions across both space and time, the model was trained using data from all 55 locations.

Clinical data (hospitalizations)

Age- and condition-specific inpatient hospitalization data were collected for 15 countries, spanning five continents, encompassing North and South America, Europe, Asia, and Oceania (Table 2). We identified all hospitalizations with primary or secondary diagnoses of respiratory or cardiorespiratory disease and aggregated across four age groups: 18–59 years, 60–74 years, ≥60 years, and ≥75 years and by week (or, in the case of Ireland, by month based on data availability). For Ireland and Japan, age group categories slightly deviated from the standard age groups and results were reported for country-specific age groups (i.e., 18–64 years, 65–79 years, ≥65 years, ≥80 years for Ireland and

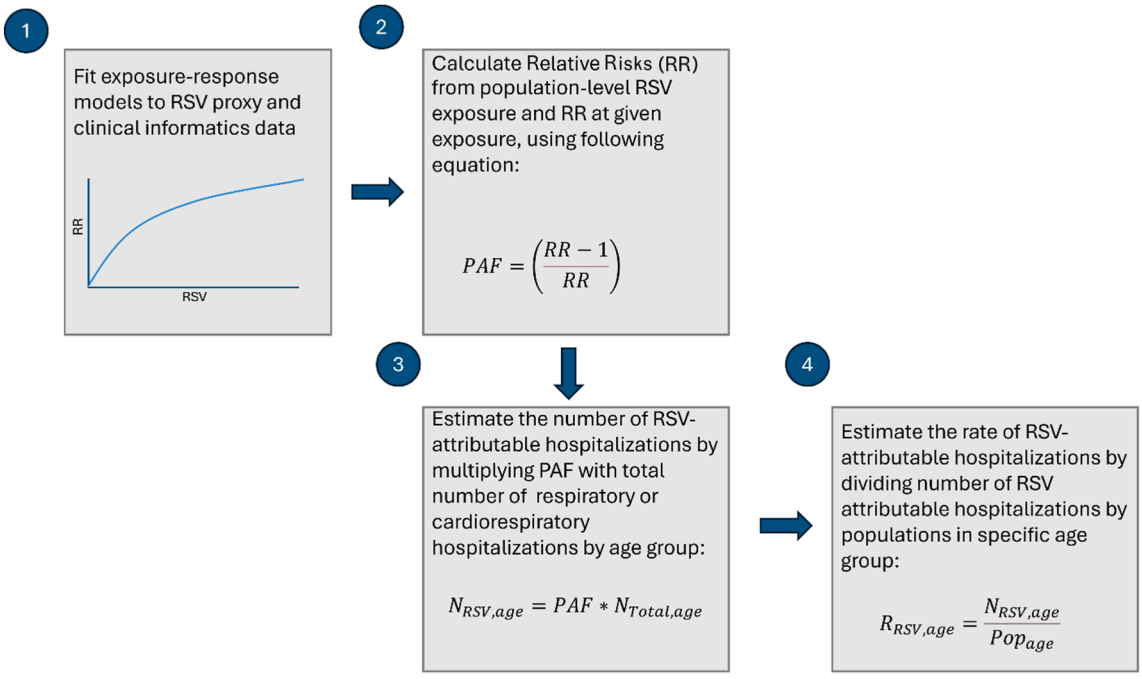

Fig. 1: Flowchart illustrating individual steps of the estimation approach.

18–59 years, 60–79 years, and ≥60 years for Japan); detailed information on age groups is included in Supplementary Table S5. All "J" ICD-10 codes were included under the "respiratory" category (J00-J99), while a narrow definition for cardiorespiratory diseases (J00-J99, I21, I48–I50, I63–I64) was applied, restricting

	Country	Start Year	End Year	# weeks with data	# missing values	% of missing weeks	Total # of samples	Average# of samples tested per week	Range[a] (% positive)	Exposure-response relationship[b]
1	Argentina[f]	2016	2019	207	1	0.5%	338,547	1636	0–40%	N/A[e]
2	Brazil[f]	2015	2019	136	125	47.9%	79,196	582	0–25%	surveillance[b]
3	Canada[f]	2015	2019	207	54	20.7%	1,377,637	6655	0–12%	surveillance (model-corrected)[c]
4	Chile[f]	2015	2019	252	9	3.4%	244,632	971	0–40%	surveillance
5	Georgia[f]	2016	2017	22	82	78.8%	1359	62	0–24%	surveillance (model-corrected)[c]
6	Germany[f]	2015	2019	256	5	1.9%	25,162	98	0–20%	surveillance (model-corrected)[c]
7	Greece[f]	2015	2019	261	0	0	13,993	54	0–16%	surveillance
8	Ireland[f]	2015	2019	258	2	1%	92,332	358	0–25%	surveillance
9	Italy[f]	2015	2016	105	0	0%	20,551	196	0–15%	surveillance (model-corrected)[c]
10	Japan[f]	2015	2019	260	260	100%	0	0	0–15%	modelled surveillance[d]
11	Mexico[f]	2016	2019	207	1	0.5%	104,330	504	0–5%	surveillance[b]
12	New Zealand[f]	2015	2019	261	0	0	6932	27	0–36%	surveillance (model-corrected)[c]
13	Poland[f]	2015	2019	130	131	50.2%	25,895	199	0–14%	surveillance (model-corrected)[c]
14	Spain[f]	2016	2019	193	15	7.7%	124,425	601	0–45	surveillance
15	United States of America[g]	2016	2019	208	0	0	15,653,646	54,925	0–16%	surveillance

[a]Range of weekly RSV positivity (%) as indicated by the percentage of samples testing positive for RSV. [b]Surveillance data were not incorporated into the final analysis of the exposure-response relationship for two countries: Brazil (no stable model fit) and Mexico (no stable/plausible model fit). [c]Model corrected surveillance data was generated using RegMod and is based on raw surveillance data and numerous covariates, including seasonality and meteorology. [d]No RSV surveillance data were available for Japan and exposure-response curves were fit to data modelled using RegMod (unlike for model-corrected surveillance data these estimates are not driven by within country observation but exclusively by data from surrounding countries and covariates). [e]For Argentina, the sample size for the cardiorespiratory and respiratory hospitalizations was too small to use to derive an exposure-response curve. As a proxy, we utilized the Chile exposure-response curve to estimate the RSV-attributable hospitalizations in Argentina. [f]Source: World Health Organization (WHO). [g]Source: US Center for Disease Control and Prevention (CDC).

Table 1: **Overview of RSV surveillance data for all ages.**

	Country	Source	Time Period	Type	Diagnoses
1	Argentina	Argentina Hospital Discharges	2010–2011	Inpatient EMR	ICD-10 (Primary diagnosis only)
2	Brazil	Brazil Hospital Information System (SIH)	1992–2016	Inpatient Claims	ICD-10 (Primary & secondary diagnoses)
3	Canada (Ontario)	Institute for Clinical Evaluative Sciences data repository	2010–2021	Inpatient Claims	ICD-10 (Primary & secondary diagnoses)
4	Chile	Chile Hospital Discharge Information System	2001–2019	Inpatient EMR	ICD-10 (Primary & secondary diagnoses)
5	Georgia	Georgia Hospital Data	2014, 2016–2017	Inpatient Claims	ICD-10 (Primary & secondary diagnoses)
6	Germany	Deutsche Analysedatenbank für Evaluation und Versorgungsforschung database	2015–2019	Inpatient Claims	ICD-10 (Primary & secondary diagnoses)
7	Greece	Greece Regional General University Hospital of Larissa Data	2012–2019	Inpatient EMR	ICD-9 (Primary & secondary diagnoses)
8	Ireland	Hospital Inpatient Enquiry (HIPE)[a]	2016–2019	Inpatient Claims	ICD-10 (Primary & secondary diagnoses)
9	Italy	Italy Hospital Inpatient Discharges	2005–2019	Inpatient EMR	ICD-9 (Primary & secondary diagnoses)
10	Japan	Medical Data Vision (MDV) database	2015–2018	Inpatient Claims	ICD-10 (Primary & secondary diagnoses)
11	Mexico	Mexico Institutions of Health Sector Hospital Discharges	2000–2020	Inpatient EMR	ICD-10 (Primary & secondary diagnoses)
12	New Zealand	New Zealand National Minimum Dataset	2000–2020	Inpatient EMR	ICD-10 (Primary & secondary diagnoses)
13	Poland	Poland National Health Fund Patient Claims	2015–2018	Inpatient Claims	ICD-9 (Primary diagnosis only)
14	Spain	National Hospital Inpatient Discharges database	2016–2019	Inpatient EMR	ICD-10 (Primary & secondary diagnoses)
15	United States	United States MarketScan Databases (Truven)	2000, 2010–2019	Inpatient Claims	ICD-10 (Primary & secondary diagnoses)

EMR = Electronic Medical Records. [a]The (HIPE) system collects information on inpatient and day-case patients discharged from Irish acute public hospitals; private hospitals are excluded.

Table 2: **Overview of respiratory and cardiorespiratory hospitalization data sources.**

to those cardiovascular conditions that are likely to be influenced by RSV. In addition, we developed an alternative proxy reflecting RSV activity in the general population, based on RSV-related diagnosis codes attached to inpatient records among children under 2 years, forth on termed as "hospital-based RSV proxy." We elected to incorporate this alternative proxy for RSV activity in the general population because RSV testing in young children is more common and has higher sensitivity than testing in adults.[6,9,25] While these diagnoses likely do not reflect the actual number of RSV cases among adults, we assume that the temporal variations in RSV-related hospitalizations in young children appropriately reflect the pattern of RSV activity in the adult population when an appropriate lag applied. Supplementary Material Table S1 identifies the ICD-9 and ICD-10 codes used to define respiratory and cardiorespiratory hospitalizations and the hospital-based RSV proxy.

To address the challenge of undefined hospital catchment areas and varying underlying populations over time, we scaled our hospitalization data to official hospitalization statistics for most countries (if these official statistics were available). This approach ensures consistency and comparability across different locations. The scaling factors were derived as follows: For Brazil, Chile, Germany, Greece, Italy, Mexico, New Zealand, Poland, and the United States, scaling factors were obtained from the OECD database, reported by official bodies such as the Ministry of Health or the Statistical Bureau in each country. For Japan, age- and year-specific scaling factors were provided by collaborators. In Canada, we assumed the hospitalization data was representative of the Ontario province and used the age-specific population in Ontario as the denominator. For Georgia, the data was representative of 90% of the population; thus, we used 90% of the Georgian population as the denominator. All location-specific modelling considerations, including sources used for scaling hospitalization data, are detailed in the location-specific model overview table (Supplementary Table S4).

Ethics

This study was approved by the Advarra Institutional Review Board (Study number Pro00068118). We obtained approval to use de-identified, aggregated clinical data from all 15 data sources included in the study. Weekly hospitalization counts for Argentina, Brazil, Chile, Georgia, Greece, Mexico, New Zealand, Poland and the United States were derived from analyses conducted by IHME and are used with permission. De-identified data for Canada (Ontario) was provided from the ICES Data Repository, maintained by the Institute for Clinical Evaluative Sciences (ICES) with support from its funders and partners, including Canada's Strategy for Patient-Oriented Research (SPOR), the Ontario SPOR Support Unit, the Canadian Institutes of Health Research, and the Government of Ontario. The opinions, results, and conclusions expressed are those of the authors and are independent of ICES and its funders. No endorsement by ICES or any of its partners is intended or should be inferred. Data from Italy was sourced from C.R.E.A. Sanità–Centre for Applied Economic Research in Healthcare S.r.l. and appropriate ethical approval was sought and granted by C.R.E.A. Sanità and Pfizer for use as part of this study. Data from Japan was sourced from Japan Medical Data Vision (MDV); data from Germany was sourced from Deutsche Analysedatenbank für Evaluation und Versorgungsforschung database; data from Ireland was

sourced from Hospital Inpatient Enquiry (HIPE) of Ireland; data from Spain was sourced from the National Hospital Inpatient Discharges database. These data were provided in an anonymized structured format and contained no patient personal information; therefore, no ethical approval was required. RSV surveillance data, collected from the WHO GISRS and other national surveillance systems, does not entail any personal information and is publicly available through the WHO GISRS platform https://www.who.int/initiatives/global-influenza-surveillance-and-response-system and the European Respiratory Surveillance Summary https://erviss.org/.

Informed consent for all participants was collected by the data providers allowing for de-identification and redistribution of the data for this study.

Statistics

Exposure-response modelling

To generate exposure-response curves displaying the relationship between RSV activity and hospitalizations, we fit country-specific generalized additive models (GAMs) adjusting for trend, season, temperature, humidity, and influenza. We excluded data after 2020 to avoid confounding by Covid-19. A GAM is a versatile statistical tool used for regression analysis, enhancing the generalized linear model (GLM) by accommodating non-linear relationships between predictor and response variables. GAMs utilize smooth functions, such as splines, to model the effects of each predictor without assuming a predefined parametric form. This makes GAMs particularly valuable for exploring and modelling data with unknown or highly non-linear underlying relationships. In our analysis, we compared the predictive power of two RSV activity proxies: (1) percentage of positive samples in RSV surveillance per week, i.e., the surveillance-based proxy and (2) number of RSV-related hospitalizations in children under 2 years per week, i.e., the hospital-based proxy. Continuous variables, including lagged RSV proxies, influenza activity, calendar week, and meteorological variables were modelled as splines. We defined three degrees of freedom for RSV proxies and influenza activity, four degrees of freedom per year for seasonal splines, and four degrees of freedom for temperature and humidity. We evaluated models based on several parameters, including significance level, adjusted R^2, and generalized cross-validation (GCV) score. To account for potential time-delayed effects of RSV exposure, we incorporated lagged RSV exposure of up to four weeks, allowing the model to select the optimal predictor based on the GCV score. To mitigate autocorrelation, we calculated weekly averages, where a four-week lag was defined as the mean of the current week and the four preceding weeks. Finally, to evaluate the robustness of our models, we adjusted the degrees of freedom for seasonality and meteorological factors, observing overall satisfactory stability.

Estimating population attributable fractions and RSV-attributable hospitalizations

Finally, we estimated PAFs and number of hospitalizations attributable to RSV for all 15 countries for hospital- and surveillance-based proxies. Estimations followed GBD standard protocol which defines PAFs as (RR-1)/RR where RR is the relative risk at a given exposure, i.e., the relative risk of hospitalization at a prevalent RSV activity in a specific location; full methods are detailed elsewhere.[22,26] RSV-attributable hospitalizations were calculated by multiplying PAFs and hospitalizations for each country, age group and proxy, and rates were calculated by dividing the RSV-attributable counts by population in each age group. Additional information on country-wide annual hospitalization estimates is provided in the Supplementary Material, Table S5. Weekly PAFs were aggregated to generate annual PAFs and RSV-attributable hospitalization by age and disease group, i.e., respiratory and cardiorespiratory outcomes.

Role of funding source

The study was sponsored by Pfizer Inc. KB, QR, CWG, SML, AO, JS are employees of IHME, which received funding from Pfizer in connection with the development of this manuscript. CL, BDG, and EB are employees of Pfizer and were involved in formulating the study questions, study design, and interpretation of the results. KB, QR, and AO had access to the data and were responsible for data analyses with input from all the other co-authors. KB wrote the manuscript and received critical feedback from CL, BDG, EB, QR, AO, CWG, JS, DB, AGG, CLa, MH, MF, AY, and SML. All authors critically reviewed the manuscript and contributed to the decision to publish its final version.

Results

Exposure-response relationships

We identified a significant and robust relationship between population-based RSV activity and increased hospitalization for respiratory and cardiorespiratory conditions across all countries. Exposure-response curves were typically non-linear, with a steeper increase in hospitalizations observed at the lower end of the RSV exposure range (Fig. 2). The quality and usability of hospital-based and surveillance-based RSV proxies varied by country. Overall, hospital-based RSV proxies were better predictors of cardiorespiratory hospitalization than surveillance-based proxies, based on goodness-of-fit measures (e.g., GCV, R^2) and model stability (Supplementary Material, Figs. S4–S17). However, hospital-based proxies could not be derived for Greece, Georgia, and Argentina due to small numbers of RSV-specific diagnoses. Additionally, in Mexico and Brazil, RSV surveillance data quality was too poor to correct, preventing a stable model fit

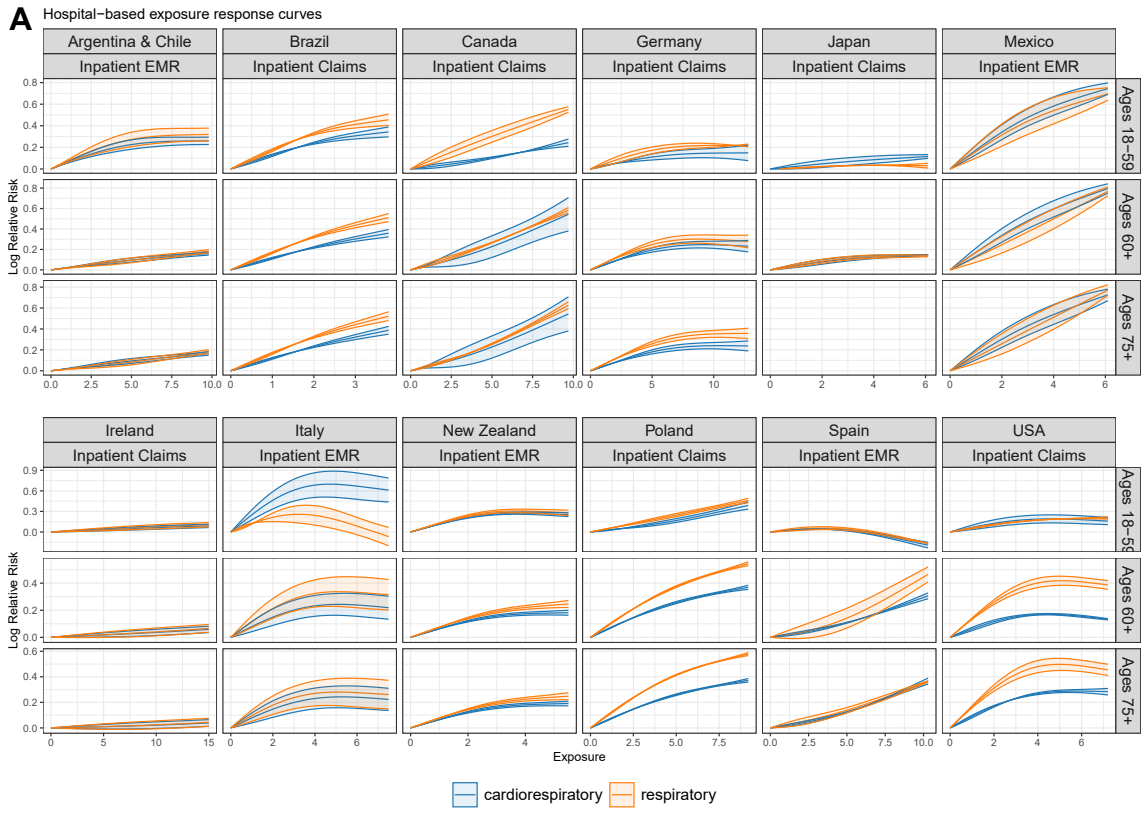

Fig. 2: Exposure-response curves displaying the relationship between RSV activity and hospitalization for respiratory and cardiorespiratory conditions by age and country. Panel A displays exposure-response curves based on hospital-based RSV proxy [N of RSV diagnoses scaled]. Panel B displays exposure-response curves based on the surveillance- and model-corrected surveillance RSV proxy [in % of positive samples].

(Supplementary Material, Figs. S2 and S3). In other countries, such as Canada, Germany, and Poland, it was possible to remediate low-quality surveillance data through model corrections, or to fully impute values using modelled data in the absence of a surveillance system, such as in New Zealand.

Population attributable fractions and RSV-attributable hospitalizations

Fig. 3A and B provide country-specific estimates of PAFs and RSV-attributable hospitalizations among adults aged 18–59 years, ≥60 years, and ≥75 years; Panel A presents estimates derived from hospital-based RSV proxies, while Panel B shows estimates made using surveillance-based RSV proxies.

The lowest PAFs (<1%) were observed in Spain and Canada for cardiorespiratory hospitalizations among the 18–59 and 60–74 age groups, respectively. The highest median PAFs were observed in Mexico and Brazil, ranging from 16.9% (95% uncertainty interval [UI]: 15.8–18.1) to 27.4% (21.8–33.5) across age groups and proxies. For the remaining countries, PAFs were distributed between the observed minimum and maximum values, with an even spread across the range. The mean PAF across all ages and proxies was 8.9% and the median PAF was 8.0%. Notably, estimated PAFs derived for surveillance- and hospital-based proxies were similar in magnitude for individual countries and age groups, while between-country differences were substantially more pronounced. We did not observe a clear age pattern for PAFs; estimated values were similar across age groups (Fig. 3, Supplementary Table S5).

Respiratory hospitalization rates attributable to RSV increased with age, with the lowest estimates for adults aged 18–59 years and highest for those ≥75 years within given countries, but with between-country variations (Fig. 3, Supplementary Table S5). In adults aged 18–59 years, the lowest respiratory hospitalization rates were found in Spain with 5.0 (95% UI: 0.8–9.3) hospitalizations per 100,000 for the hospital-based proxy, while the highest hospitalizations rates were observed in Germany with 101.0 (44.3–161.4) hospitalizations per 100,000 for modelled surveillance proxies. For adults ≥60 years, the lowest respiratory hospitalization rates were observed in Argentina and Chile with 43.8

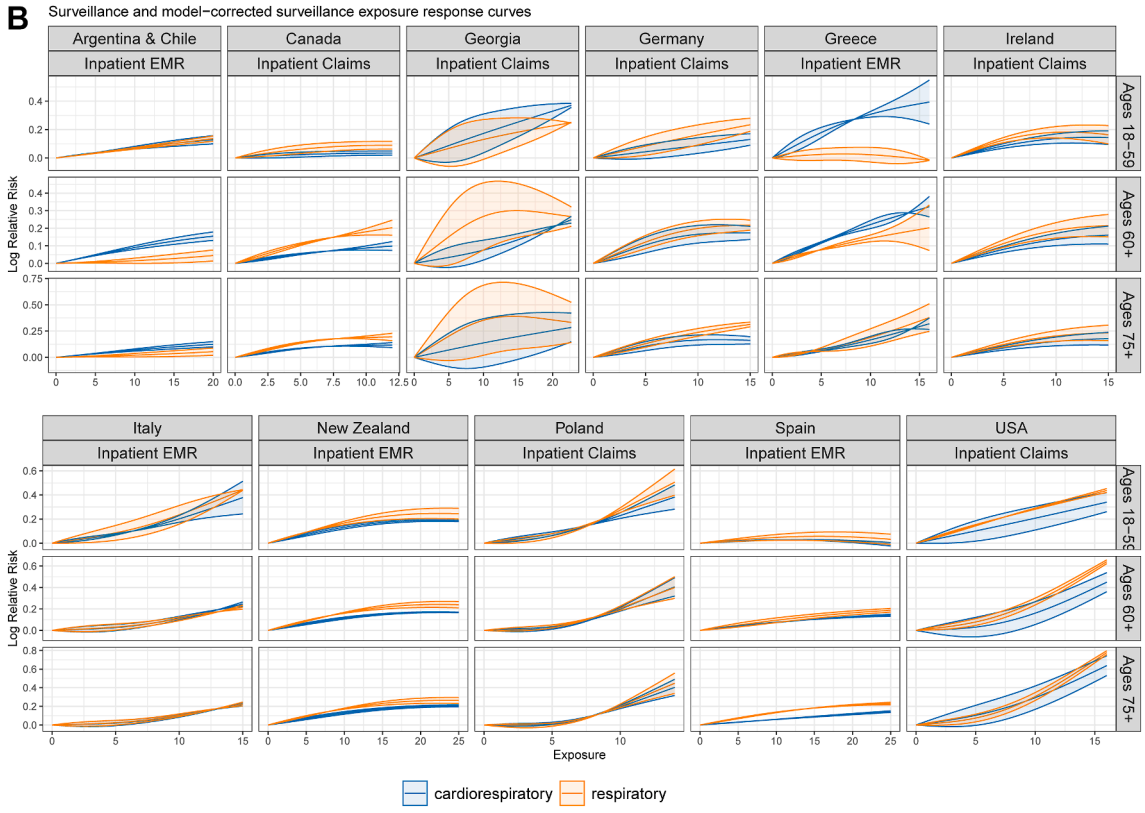

Fig. 2: Continued.

(26.2–61.8) and 44.6 (24.3–65.5) hospitalizations per 100,000, respectively, derived from surveillance-based proxy; while the highest hospitalizations were found in Germany with 397.0 (350.1–445.4) and 460.8 (337.0–589.3) per 100,000 for hospital- and surveillance-based proxies, respectively. RSV-attributable hospitalization rates were comparably high in the United States with 381.7 (352.8–411.4) for the hospital-based proxy, in New Zealand with 368.9 (337.6–400.9) for modelled surveillance data, and in Brazil with 314.4 (299.9–329.2) per 100,000 for hospital-based proxy in the same age group. For adults ≥75 years, we found the lowest RSV-attributable respiratory hospitalization rates in Argentina and Chile for the surveillance-based proxy with 110.9 (66.9–156.1) and 115.2 (64.3–167.6) hospitalizations per 100,000, respectively. The highest hospitalizations in the same age group were observed in New Zealand with 725.3 (662.7–789.6) hospitalizations per 100,000 for modelled surveillance data, in Germany with 698.4 (553.1–848.3) for model-corrected surveillance data, and in Brazil with 691.6 (658.1–725.9) hospitalizations per 100,000 for the hospital-based proxy (Fig. 3, Supplementary Table S5).

As with respiratory hospitalizations, cardiorespiratory hospitalization rates attributable to RSV increased with age. The lowest rates among those aged 18–59 years were observed in Spain for the hospital-based proxy with 5.0 (95% UI: 0.8–9.3) hospitalizations per 100,000, while the highest rates were found for Greece with 155.0 (131.9–178.9) hospitalizations per 100,000 for the surveillance-based proxy. In the ≥60 years age group, the lowest rates were found in Argentina with 91.2 (82.0–100.5) hospitalizations per 100,000 for hospital-based proxies. The highest rates for cardiorespiratory diagnoses for the same age group were found in Germany with 692.8 (434.4–962.7) hospitalizations per 100,000 for the modelled surveillance-based proxy and in Poland with 612.8 (593.2–632.5) hospitalizations per 100,000 for the hospital-based proxy. Comparably high RSV-attributable cardiorespiratory admission rates were found in the ≥60 years age group in Greece with 539.8 (499.4–580.8) hospitalizations per 100,000 for the surveillance-based proxy and in Mexico with 533.1 (419.8–653.8) hospitalizations per 100,000 for the hospital-based proxy. In the ≥75 years age group, the lowest rates were observed in Argentina and Chile with 166.8 (144.9–188.9) and 214.4 (185.2–244.0) hospitalizations per 100,000, respectively, for the surveillance-based proxy. The highest admission rates for this age group were observed in New Zealand with 1199.8

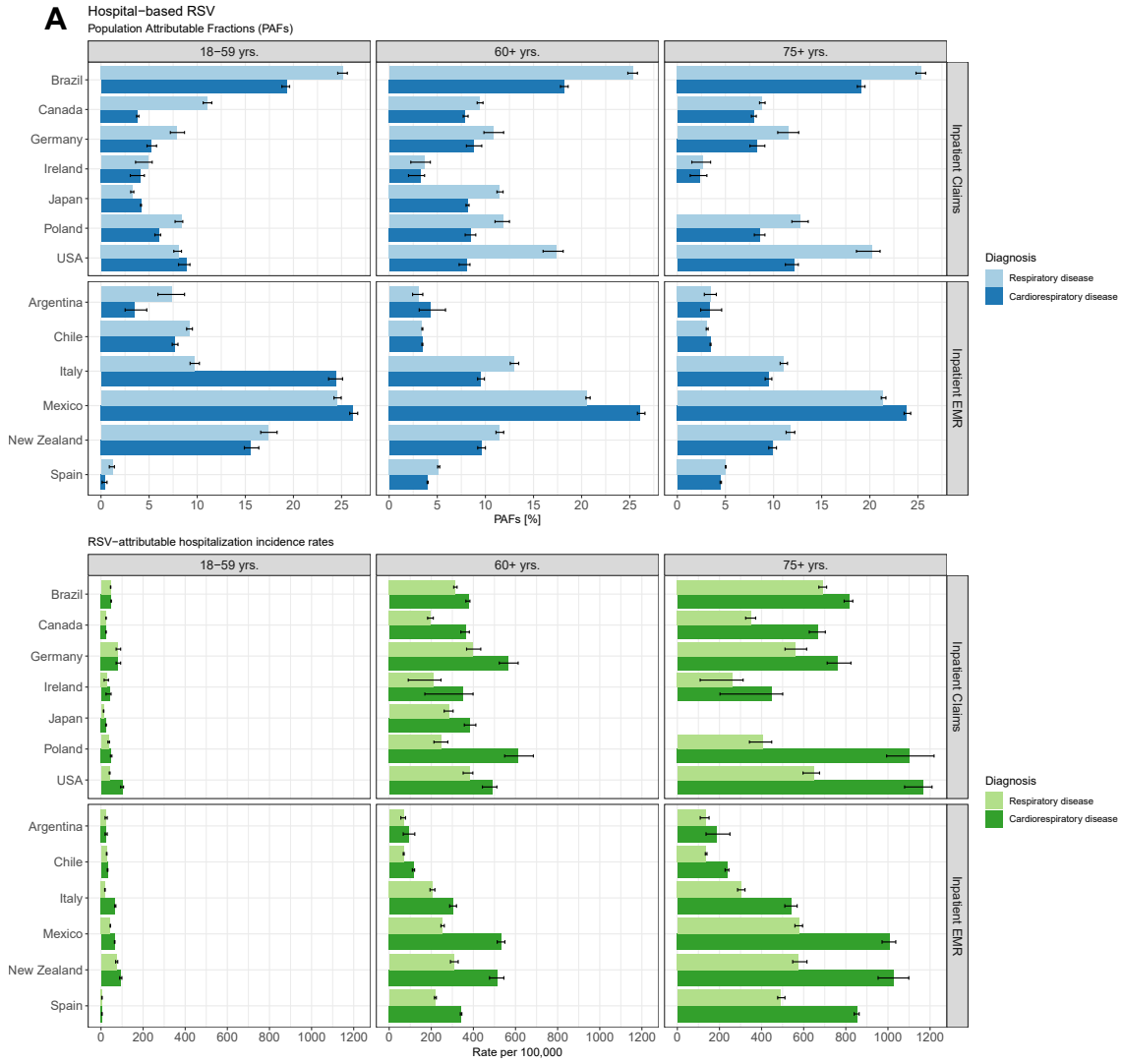

Fig. 3: PAFs and RSV-attributable hospitalization rates for surveillance- and hospital-based proxies for adults by age group. Panel A displays findings based on hospital-based RSV proxy and panel B for surveillance-based RSV proxy.

(1087.0–1313.8) for modelled surveillance proxies, and the United States with 1164.6 (1093.3–1236.4) as well as and Poland with 1102.3 (1070.9–1133.8) hospitalizations per 100,000 for hospital-based proxies (Fig. 3, Supplementary Table S5).

We did not observe pronounced year-to-year changes in country-specific PAFs or RSV-related hospitalization rates within countries; differences between countries far exceeded inter-annual changes (Fig. 4, Supplementary Material Fig. S32).

Discussion

The introduction of RSV vaccines available to adults, including the oldest adults, has revitalized the need for reliable RSV burden estimations. Our study estimated RSV-attributable hospitalizations among adults across 15 countries spanning five continents, utilizing the CRA framework integral to GBD risk factor analyses. This methodological framework integrates several innovative approaches designed to improve accuracy, reliability, and analytical consistency.

In general, the estimates of RSV-attributable hospitalization rates generated by our study are consistent with previous studies. In a recent meta-analysis, McLaughlin et al.[15] found an adjusted pooled annual rate of 267 (95% CI: 228–306) hospitalizations per 100,000 in adults aged 65 years and older and 236 (144–327) hospitalizations per 100,000 when only including model-based time-series analyses (similar to

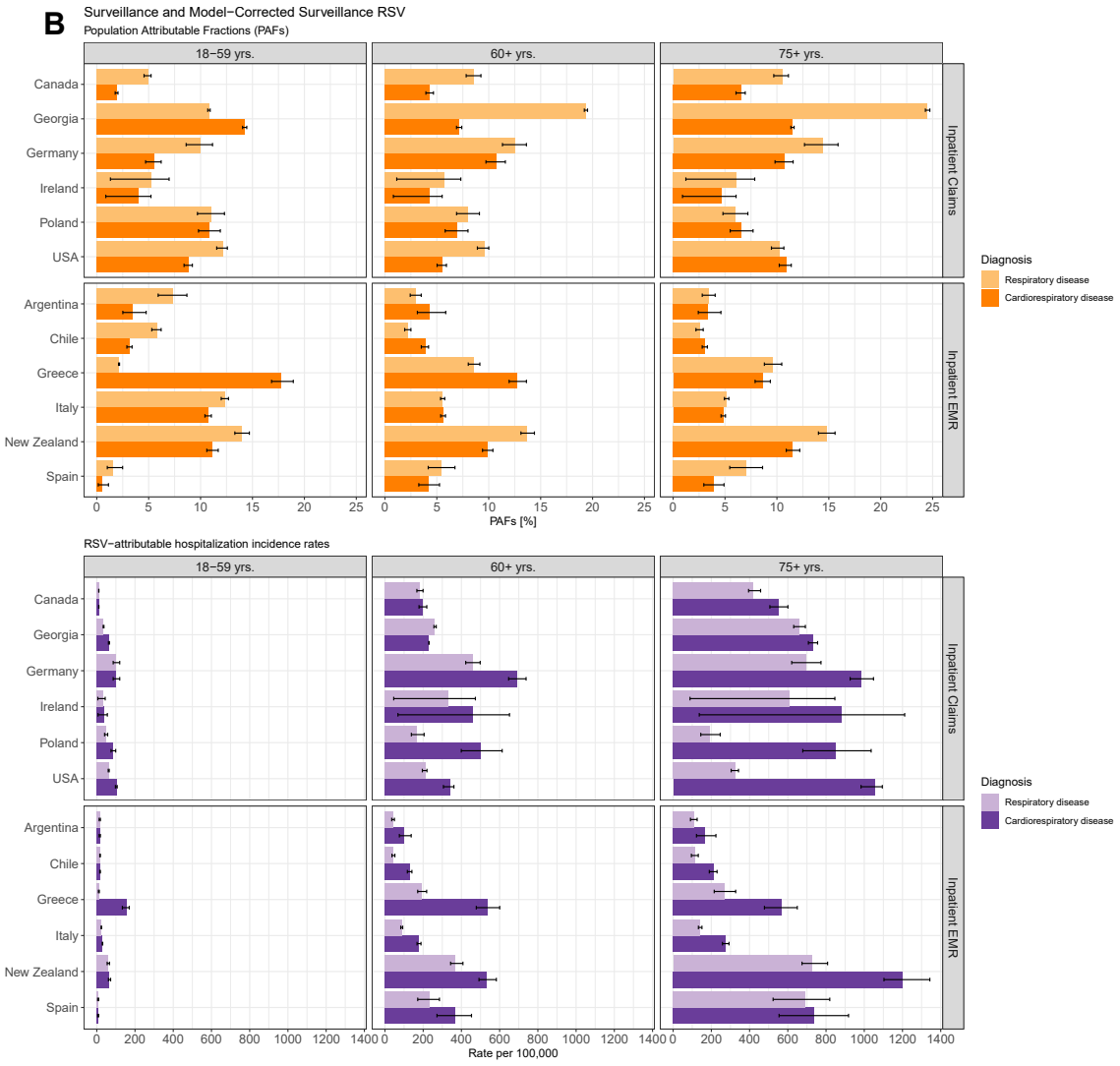

Fig. 3: Continued.

our research design). In our study, we estimated 211.3 (95% UI: 164.9–258.8) RSV-attributable respiratory hospitalizations per 100,000 adults aged ≥60 years in the USA using the surveillance-based proxy. For the hospital-based proxy, our estimates were higher with 381.7 (352.8–411.4) respiratory hospitalizations in adults older than 60 years. In a recent study, Zheng et al.[27] analyzed RSV-related respiratory hospitalizations in adults ≥60 years across New York, New Jersey, and Washington DC (2005–2014), finding rates of 130–960 per 100,000 across socioeconomic groups, largely consistent with our results. The aforementioned studies focused solely on respiratory hospitalizations, whereas our estimates for RSV-related cardiorespiratory hospitalizations in the USA are higher, with an average rate of 488.8 (439.0–539.1) per 100,000 in adults ≥60 years, highlighting RSV's impact on cardiovascular disease.

Li et al.'s[5] meta-analysis of RSV-associated acute respiratory infection hospitalizations in older adults (≥65 years) in high-income countries, based on 12 studies (eight in the USA, two in Finland, two in New Zealand), reported an adjusted rate of 347 per 100,000 (95% CI: 203–595), comparable with our estimates for the USA and New Zealand using the hospital-based proxy. Osei-Yeboah et al.[28] conducted an extrapolation study based on six northern European countries as reported in Johansen et al.[29] Across 28 EU countries, annual RSV hospitalization rates averaged 299 (256–342) per 100,000 in adults ≥85, but differences in age categories and outcomes limit direct comparison. Our findings indicate a potentially greater impact. In a

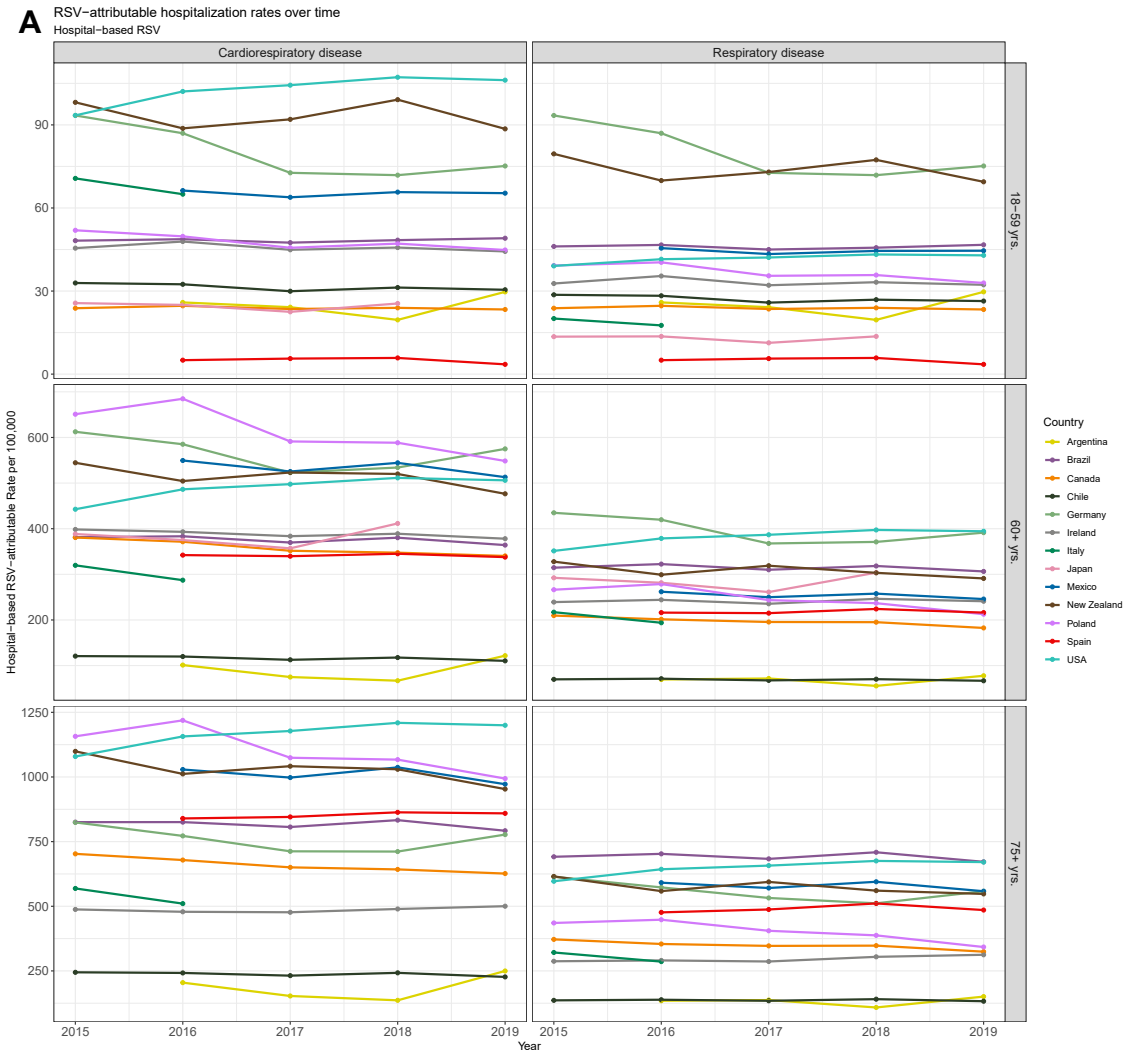

Fig. 4: Time series of RSV-attributable hospitalizations by country and age group from 2015 to 2019 for hospital-based proxy (Panel A) and surveillance-based RSV proxy (Panel B).

recent study, Polkowska-Kramek et al.[30] estimated RSV-related hospitalizations in Germany from 2017 to 2019 for adults ≥75 years, reporting 970–1486 cardiorespiratory and 571–852 respiratory hospitalizations per 100,000. Our estimates, albeit slightly lower, align with averages of 759.5 (95% UI: 678.6–842.5) cardiorespiratory and 557.7 (510.6–606.2) respiratory hospitalizations in Germany in this group using the same hospital-based proxy. Haeberer et al.[31] estimated RSV-related hospitalizations in Spain for adults ≥60, with rates of 256.9–282.9 per 100,000 for respiratory diseases and 437.6–475.8 for cardiorespiratory diseases. Our slightly lower estimates of 217.8 (96–346.1) respiratory and 341.2 (302.2–380.5) cardiorespiratory hospitalizations in Spain align with these findings, using the similar hospital-based proxy, but a narrower definition of cardiovascular disease.

Interestingly, our study found very high PAFs in (sub)tropical regions such as Mexico and Brazil ranging from 16.9 (95% UI: 15.8–18.1) to 27.4% (21.8–33.5) across age groups and proxies. Although overall RSV-attributable hospitalization rates in these countries fell within the mid-range compared to other countries due to generally lower total hospitalization numbers, our findings highlight the significant impact of RSV in these climates. In tropical and subtropical climates, RSV displays a more variable seasonal pattern with a longer RSV season and multiple peaks around the year compared to mid-latitude countries with moderate climates. The absence of distinct summer and winter seasons, coupled with consistently high humidity throughout the year, suggests that the virus may circulate continuously. Supplementary Material, Figs. S2 and S3 illustrate the bimodal distribution of

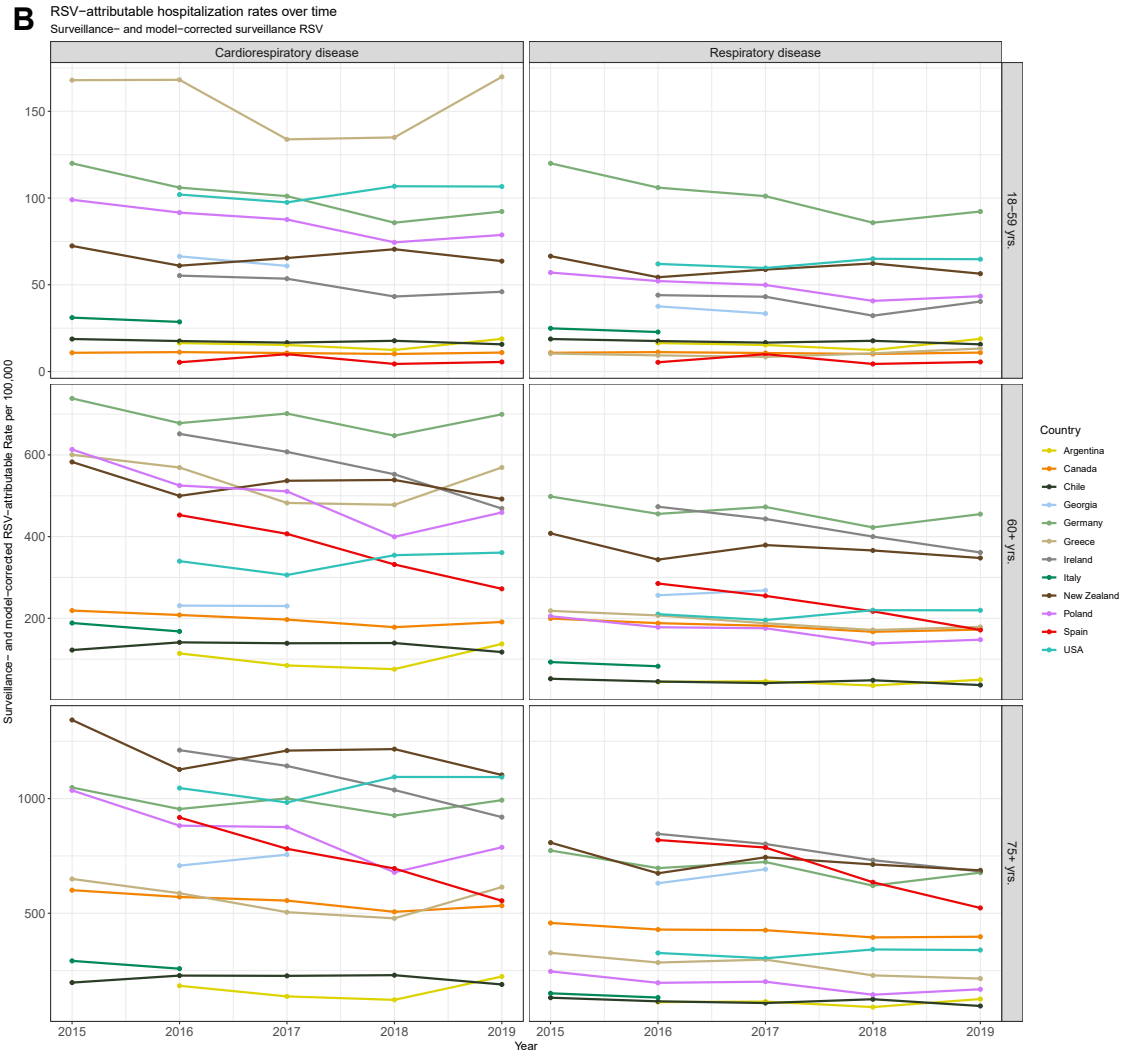

Fig. 4: Continued.

RSV in Mexico and Brazil and clearly indicate that RSV activity does not drop to the same levels as in colder climates (e.g., Chile) suggesting a mild viral activity pattern year-round. To date, there is limited research on the impact of RSV in tropical and subtropical regions. However, our study highlights the significance of RSV in these areas and underscores the need for further investigation to inform public health strategies tailored to these climates. Identifying the unique transmission dynamics in these regions, improving early detection, and guiding the development of targeted vaccination and prevention programs will ultimately help in reducing the burden of RSV on vulnerable populations.

This study features multiple strengths. First, it represents the first comprehensive estimation of RSV-attributable hospitalizations across 15 countries spanning five continents: North America, South America, Europe (both Western and Eastern), Asia, and Oceania. Utilizing a coherent methodological framework, our analysis includes several locations and climates for which no previous estimates were available, such as Brazil and Mexico, and allows comparability across locations and time periods. Second, a key innovation of this study is the ability to capture non-linear exposure-response relationships between RSV and hospitalizations. Unlike other studies that typically include a linear predictor,[13,27,31–35] our approach employs Bayesian non-parametric estimation of exposure-response curves. This non-parametric estimation of viral impacts allows the exposure-response function to follow the data and reflect any non-linearities, particularly typically steeper increases at lower exposure levels and gradual leveling off at higher levels. In addition, our study incorporates multiple confounders, including atmospheric variables

such as temperature and humidity, which have been demonstrated to significantly impact human health, morbidity, and mortality.[36] Similar to our exposure-response model, we also use non-parametric estimation to model confounders, flexibly capturing patterns and trends that do not conform to linear or sinusoidal forms. Notably, Zheng et al.[27] is the only study that compares both sinusoidal and non-parametric seasonal adjustment methods, finding a superior model fit with non-parametric adjustment. Through this sophisticated accounting for confounders, we reduce noise in the data, allowing for more precise attribution to RSV and ensuring that the effect is not falsely attributed to other factors.

Third, our analysis encompasses respiratory as well as cardiorespiratory diseases, unlike most other studies that concentrate solely on acute respiratory infections. Our broad focus allows us to capture a more comprehensive picture of the impact of RSV. The inclusion of cardiorespiratory health effects is particularly noteworthy, as it adds a new dimension to the literature that underscores the impact of infectious diseases on heart disease. Previous research has indicated that respiratory viruses, including RSV, can worsen chronic cardiovascular diseases like coronary artery disease and can trigger new cardiovascular events.[12,31] Furthermore, RSV has the potential to induce inflammation and immune dysregulation, which may contribute to atherosclerosis and lipid accumulation.[13] It has been associated with exacerbations of heart failure, arrhythmias, and myocardial infarction (MI) in patients, regardless of whether they have pre-existing cardiovascular conditions.[12] Additionally, several studies have reported a significant prevalence of underlying coronary artery disease and congestive heart failure among patients affected by RSV, particularly in those hospitalized due to the infection.[12]

Fourth, our study also contributes meaningfully to the discourse on surveillance data quality by comparing surveillance-based and hospital-based RSV proxies. RSV surveillance systems were significantly scaled up over recent years, particularly since the initiation of the WHO-RSV surveillance system in 2015. Even though our study relied on the most recent RSV surveillance after 2015, we found mixed quality and usability of surveillance data for health impact assessment. Overall, we achieved better and more stable model fits when using the hospital-based proxy as compared to the surveillance-based proxy. In Brazil and Mexico, no model fit could be achieved using a surveillance-based proxy, suggesting data quality is either poor or the country-wide indicator does not capture RSV circulation in these geographically and climatologically diverse countries. In six additional countries—Canada, Georgia, Germany, Poland, Italy, and New Zealand—we had to rely on model-corrected RSV data to generate a stable exposure-response relationship. In Chile, the surveillance-based and hospital-based proxies were highly correlated and estimates for RSV-related hospitalization were nearly identical for both indicators. This suggests that high-quality surveillance data is potentially capable of capturing the health-relevant circulation of RSV. Nonetheless, we also need to acknowledge that differences in coding practices (between countries, hospitals or medical staff) might limit the usability of the hospital-based proxy.

Despite these strengths, we also need to acknowledge the limitations inherent to all epidemiological studies based on an ecological research design, which include potential ecological fallacies, unmeasured confounding variables, and the lack of individual-level data. By utilizing high-quality data and adjusting for numerous potential confounders with a sophisticated statistical model, we have mitigated these limitations to the best of our ability. Another limitation of our study emerges for climatologically diverse countries, such as the USA or Brazil. Our aggregated data may not reflect regional differences in RSV circulation across the country, possibly introducing noise and increasing uncertainty. Nonetheless, in the absence of individual data and routine RSV testing or high-resolution ecological data, we believe that our enhanced framework provides a reliable approach for estimating the large-scale impact of RSV. It is also important to note differences in hospitalization utilization across countries. Overall hospitalization rates, including those for respiratory and cardiorespiratory diseases, vary substantially between nations. To illustrate these discrepancies, in 2019, 1601.7 hospital admissions per 100,000 population were reported for respiratory diseases in Germany, whereas only 193.7 per 100,000 admissions were recorded in Mexico during the same year.[37] Hospitalization rates are not solely indicative of the underlying disease burden as they may also be influenced by country-specific medical practices, healthcare system capacity, and the availability of services. Consequently, our estimated RSV-attributable hospitalization rates do not purely reflect the burden of RSV but are also shaped by overall hospitalization patterns. In contrast, the PAF—the proportion of hospitalizations attributable to RSV—may offer a more accurate measure of the virus's impact. This distinction is particularly evident in countries such as Mexico and Brazil, where high PAFs are observed despite moderate RSV-attributable hospitalization rates, a result of generally lower hospitalization rates across the healthcare system. In countries, with similar healthcare systems and admission practices, comparisons of RSV-attributable hospitalization rates should reflect variations in the underlying health status of the population.

In summary, this research offers a robust foundation for understanding RSV-attributable hospitalizations globally. The novel methodological framework and inclusion of diverse climatic regions provide

valuable insights for future global health models and policies. By leveraging high-quality surveillance data from 2015 onwards and adopting a comprehensive hospitalization analysis, our study provides a nuanced understanding of RSV's impact on both respiratory and cardiorespiratory diseases. This holistic perspective is crucial for informing public health strategies—particularly whether and how to use new interventions—and advancing our knowledge of RSV's broader health implications.

Contributors

KB, CL, EB, BDG and CWG conceptualized and designed the methodological approach. QR, AO and KB conducted the analyses and modelling and had access to and have verified the underlying data. KB led the manuscript writing, with contributions from QR, CWG, and SML. KB, CL, AO, JS, BDG, EB, DB, MF, AGG, MH, CLa, and AY collectively contributed to the interpretation of research findings and provided critical feedback on the manuscript. All authors have read and approved the final manuscript.

Data sharing statement

To download the data used in these analyses, please visit the Global Health Data Exchange GBD 2021 website at http://ghdx.healthdata.org/.

Editor note

The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Declaration of interests

KB, QR, JS, AO, SML, and CWG are employees of the Institute for Health Metrics and Evaluation (IHME), a public health research institute of the University of Washington in Seattle. The mission of IHME is to deliver to the world timely, relevant, and scientifically valid evidence to improve health policy and practice. CL, BG, MF, AG, CLa, AY are employees of Pfizer, and Pfizer provided funding to support the development of the present manuscript; BDG, MH and DB were employees of Pfizer at the time of manuscript development. CL, BDG, DB, MF own Pfizer stock.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103292.

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