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Title: Age-specific estimates of Respiratory Syncytial Virus-associated hospitalizations in 6 European countries: A time series analysis.

Running title: RSV-associated hospitalizations

Authors: Caroline K. Johannesen[a], Maarten van Wijhe[a], Sabine Tong[b], Liliana V. Fernández[c], Terho Heikkinen[d], Michiel van Boven[e], Xin Wang[f], Håkon Bøås[g], You Li[f], Harry Campbell, John Paget[i], Luca Stona[j], Anne Teirlinck[e], Toni Lehtonen[k], Hanna Nohynek[k], Mathieu Bangert[l] and Thea K. Fischer[m,], For the RESCEU investigators[l].

[l] Members of the RESCEU investigators group are listed at the end of the text.

Author affiliations:

[a]Statens Serum Institut, Copenhagen, Denmark

[b]Sanofi, Chilly-Mazarin, France

[c]Department of Methods Development and Analytics, Norwegian Institute of Public Health, Oslo, Norway.

[d]Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland

[e]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands

[f]School of Public Health, Nanjing Medical University, Nanjing, China

[g]Department of Infection Control and Preparedness, Norwegian Institute of Public Health, Oslo, Norway.

[h]Centre for Global Health, Usher Institute, University of Edinburgh

[i]Netherlands Institute for Health Services Research (Nivel), Utrecht, the Netherlands

[j]Fondazione Penta ONLUS, Padova, Italy

[k]Department of Health Security, Finnish Institute for Health and Welfare (THL), Helsinki, Finland

[l]Sanofi Pasteur, Lyon, France

[m]Deptartment of Clinical Research, Nordsjællands University Hospital, Hilleroed, Denmark

Corresponding author: Caroline Klint Johannesen, Statens Serum Institut, Copenhagen Denmark.

Email: cakj@ssi.dk, telephone: +45 2544 7557

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Abstract

Background: Knowledge on age-specific hospitalizations associated with RSV infection is limited due to limited testing, especially in older children and adults in whom RSV infections are not expected to be severe. Burden estimates based on RSV-coding of hospital admissions are known to underestimate the burden of RSV.

Objective: We aim to provide robust and reliable age-specific burden estimates of RSV-associated hospital admissions based on data on respiratory infections from national health registers and laboratory confirmed cases of RSV.

Methods: We conducted multi-season regression analysis of weekly hospitalizations with respiratory infection and weekly laboratory-confirmed cases of RSV and influenza as covariates, based on national health registers and laboratory databases across six European countries. The burden of RSV-associated hospitalizations was estimated by age group, clinical diagnosis and presence of underlying medical conditions.

Results: Across the six European countries, hospitalizations of children with respiratory infections were clearly associated with RSV, with associated proportions ranging from 28% to 60% in children younger than three months and we found substantial proportions of admissions to hospital with respiratory infections associated with RSV in children younger than 3 years**.** Associated proportions were highest among hospitalizations with ICD-10 codes of 'bronchitis and bronchiolitis'. In all six countries, annual incidence of RSV-associated hospitalizations was >40 per 1000 persons in the age group 0-2 months. In age group 1-2 years the incidence rate ranged from 1.3-10.5 hospitalizations per 1000. Adults above 85 years had hospitalizations with respiratory infection associated to RSV in all six countries though incidence rates were low.

Conclusion: Our findings highlight the substantial proportion of RSV infections among hospital admissions across different ages and may help public health professionals and policy makers when planning prevention and control strategies. In addition, our findings provide valuable insights for health care professionals attending to both children and adults presenting with symptoms of viral respiratory infections.

Keywords: Respiratory syncytial virus, Viral hospitalizations, Burden of disease, RSV, Public Health, Time series analysis

Introduction

Respiratory syncytial virus (RSV) is a small single-stranded RNA virus recognized as the leading cause of hospitalization among children with lower respiratory tract infections [1]. The burden of RSV-infections among young children has been well investigated in recent years [2-4] though problems with RSV coding of hospital admissions have been shown to result in underestimation of disease burden as a result of low sensitivity [5,6]. Due to the documented global disease burden, development of safe vaccines against RSV has been a priority globally. The ongoing work towards RSV vaccines has also made surveillance of RSV and establishment of robust age-specific burden of disease estimates a high priority by WHO [7]. It is therefore highly relevant to document valid estimates for the age-specific RSV burden.

Specifically, in adults, the knowledge of the burden of RSV infections is limited due to the lack of routine testing for RSV. This results in only the most severe cases being detected [8,9,10]. However, the burden of disease due to RSV infection can be substantial. In a 2015 study of the RSV burden in the United Kingdom based on UK national registry data, 1.4% of all hospitalizations with respiratory disease in adults aged 18-45 were found to be associated with RSV, while 5.2% and 5.8% were attributed to RSV in age groups 50-64 and 65-74, respectively [11].

We aimed to assess the age-specific burden of RSV on hospitalizations with respiratory infections across several European countries, and to assess this burden within four ICD-10 code based respiratory diagnostic groups. To this end, we apply time-series models that help mitigate the existing lack of testing. Such models have long been used to assess the burden of influenza [12-14] and have found traction in RSV burden modelling as well [11,15-17]. Time-series modelling uses seasonal variations in the circulation of RSV, influenza A and influenza B, to attribute outcomes (e.g. hospital admissions, mortality) to these pathogens.

Estimates of RSV hospital burden from young infants to the elderly will help guide health resource allocation, prevention strategies, further disease surveillance, as well as provide an input for impact studies for future RSV prophylactic interventions including vaccines and monoclonal antibodies.

Methods

Study design

We performed retrospective registry and population-based modelling studies in six European countries: Denmark, England, Finland, Norway, the Netherlands and Scotland. Our study builds upon a previous investigation of RSV admissions [4] and adds to existing burden estimates based on RSV-coded admission by statistical associations of virus in circulation and hospitalizations, working against known underreporting of RSV in hospital admissions. In our study, available data ranged from 2006 to 2018. Our objective was to estimate age specific annual proportions and incidence rates of hospital admissions associated with RSV using routinely collected data extracted from national registries. Among patients aged 17 and younger, we also investigated proportions and incidence rates of hospital admissions associated with RSV among a high-risk group composed of premature children (gestational age <37 weeks) and children with cystic fibrosis, congenital heart disease, bronchi-pulmonary dysplasia and Down syndrome. The data collection and analyses were performed locally and the extraction process as well as definitions were standardized[4].

Data sources

Since 1995 ICD-10 codes have been used to classify diagnoses in most of Europe. In this study we identified all respiratory hospital admissions during the period 2006 to 2018 using the ICD-10 codes listed in the supplementary Table 1. A hospital admission was defined as any admission that contained at least one respiratory infection-specific ICD-10 code at any point during admission. Acute inpatient and day cases were included, while admissions recorded as scheduled or routine were not included.

Collectively, each region utilized national or regional hospitalization registry systems to extract respiratory hospital admissions. These data were linked to other sources such as birth records and civil records using personal identification numbers where these data were available. In addition to these data sources, information from positive respiratory viral tests was obtained from registers and laboratories in each country, to describe pathogen circulation in the society. The primary data sources for hospital admissions have been described before [4] and all data sources are described in the supplementary material including age-stratified estimates (supplementary table 2 and supplementary figure 2).

Method of analyses

Multiple linear regression models were used to estimate the number of hospital admissions due to infections with RSV, influenza A and influenza B within each of the following diagnostic groups: acute upper

respiratory tract infections (AURTI), pneumonia and influenza, bronchiolitis and bronchitis, and unspecified lower respiratory tract infection (LRTI). Influenza A and B viruses were included in the model, as they are pathogens highly associated with hospitalizations for which testing is performed routinely. Hospital admissions were stratified by the following age groups to give a detailed description of infant and young childhood years and investigate if the proportion of RSV hospitalizations are different in multiple age groups above 65 years: 0-2 months, 3-5 months, 6-11 months, 1-2 years, 3-4 years, 5-17 years, 18-64 years, 65-74 years, 75-84 years, and 85+ years. Separate models were fit for each country, age group and diagnostic group and risk group, and each research team conducted separate analyses (data availability, supplementary table 2. Final models, supplementary figures 5).

The model fitting was done in a tiered approach; a base model was fitted to the weekly number of hospital admissions for the respective region, age group and diagnosis and risk group, as dependent variable, and the weekly number of laboratory-confirmed cases of RSV, influenza A and influenza B were the independent variables in a manner similar to previous work on RSV associations [11]. From this model a forward selection process was initiated, to enhance the model with seasonal and secular trend terms.

For all age groups and outcomes, the base models thus followed the form of

$$Y=\beta_0+\beta_{p1}RSV+\beta_{p2}InfluenzaA+\beta_{p3}InfluenzaB$$

Time trends were added to the base model, where we ran all the combinations of these: A linear trend ($B_{s1}t$), a seasonal trend ($\beta_{s4}\sin(2\pi t/52.25)+\beta_{s5}\cos(2\pi t/52.25)$) and a polynomial trend ($\beta_{s1}t+\beta_{s2}t^2+\beta_{s3}t^3$)

After assessing the best fitting base model with time trends, we tested the introduction of terms lagged 1 to 3 weeks of the pathogen variables ($\beta_{p1,t-k}RSV+\beta_{p2,t-k}InfluenzaA+\beta_{p3,\,t-k}InfluenzaB$) with k as the number of lagged weeks.

To account for potential changes in testing practice following the 2009 influenza A/H1N1 pandemic, a variable indicating pre- or post-pandemic was included in the model: βs7Pandemic, and interactions between pathogens in the final model and pre-pandemic indicator were investigated if the regional data included admissions from before week 20 of 2009. The best model fit was assessed by the lowest AIC value. The final models differed between age and diagnosis group but were almost consistently ending at inclusion of time in polynomial or seasonal trend. In models for children under 5, RSV were mostly included

without a lag time, while RSV lags of three weeks were most common in age groups above age 5, with no clear differences within the diagnostic groups. Distribution of model elements are depicted in supplementary figures 5 and 6.

Estimates of hospital admissions associated with RSV (including 95% CIs) were calculated by multiplying the coefficient from the final models by the total number of weekly laboratory-confirmed episodes of RSV. Annual incidence rates for RSV-associated admissions were calculated using mid-year population estimates by age group. No incidence estimates are presented for the high-risk groups due to lack of data on population size. We opted to present all model parameter estimates without regards to the biological plausibility; i.e. also negative estimates are presented. However, due to the implausibility, we excluded negative estimates from calculations of proportions and incidence rates of hospitalizations due to RSV. Specifically, negative coefficients for RSV are interpreted as a null result meaning that no hospital admissions could be attributed to RSV. Where calculation of proportions with our estimates exceeded proportions of 100%, we reported these findings despite the implausibility. All analyses were performed in the R Statistical Software [18].

Results

Hospitalizations with all respiratory infections associated with RSV

Among all hospital admissions with respiratory infection the highest proportions of RSV-associated admissions were found in age group 0-2 months, ranging from 28.1% in Norway to 60.9% in the Netherlands (Figure 1). In general, all countries showed a pattern of high rates among children younger than 3 years, falling to no admissions due to RSV in ages 5-17 years. No admissions were associated with RSV in 18-64-year-olds in Scotland, Finland, Norway, the Netherlands and Denmark, and to 65-74 years and 75-84 years in Denmark.

The average yearly incidence of hospital admissions associated with RSV, by age and country, are shown in Figure 2. In the youngest age group, 0-2 months, we estimated that in all countries over 40 hospital admissions per 1000 population (range 42-90 per 1000) were associated with RSV (Table 1). Overall, the incidence declined with age, and increased again in those aged 65 and over (Figure 2, Table 1). Incidence rates in age group 85+ years were similar to those of children 1-2 years in Scotland (1-2 years 5.1 and 85+

5.0 per 1000 per year), England (1-2 years 7.5 and 85+ 6.0 per 1000 per year), and the Netherlands (1-2 years 1.3 and 85+ 3.1 per 1000 per year), The incidence of RSV associated hospitalizations show the proportion of the age specific population of a country that are hospitalised with association to RSV pr 1000 in an average year, where the proportion of admission show how many of the average yearly admission that we can associate with RSV.

A sensitivity analysis with age-stratified laboratory data was conducted in Norway. *Comparing to the Norwegian results from our* main analysis a lower association with RSV in age groups younger than 1 year and older than 65 years, but higher association in older children and adults (supplementary table 9).

In the high-risk population, the proportion of hospitalizations attributed to RSV varied between countries. In Scotland and England, associated fractions were generally lower in the high-risk population compared to the general population, but in Norway and Denmark they were generally higher in the high-risk population than in the general population (supplementary Table 8). Only in England, attribution to RSV was possible in age groups 5-17 years with high risk.

The estimated numbers of hospitalizations associated with RSV varied between seasons (Supplementary Figures 3 and 4).

Hospitalizations associated with RSV within diagnostic groups of respiratory infections

The association to RSV was low in hospitalizations with AURTI. No admissions were associated with RSV in the age group 5-17 years for AURTI. For all but England and the Netherlands, age groups 18-64 years and 65-74 years also had no association from RSV to AURTI. In Denmark, only age groups 1-2 years and 85+ years showed some association to RSV among the AURTI admissions, while in Finland, England and Norway all age groups under 3 years had positive associations (Figure 1B and supplementary table 4).

Within hospitalizations for ‘pneumonia and influenza’, the estimated RSV associations differed considerably between countries. In Denmark, around 48% were associated to RSV in the age group 1-2 years and no admissions were associated among children above 5 years and adults, while Scotland and England both found higher proportions of hospitalizations with ‘pneumonia and influenza’ in the adult population than among children older than 2 months (Figure 1C and supplementary table 5). In all countries, a substantial

proportion of hospitalizations with ‘pneumonia and influenza’ were associated to RSV in age group 0-2 months.

Interestingly, while no respiratory hospitalizations were associated with RSV in the age group 5-17 years in any of the countries, all countries but Finland found between 6.2 and 32.7% of ‘bronchitis and bronchiolitis’ admissions associated with RSV in this age group (Figure 1D and supplementary table 6). In age groups 0-2 months and 3-6 months, the ‘bronchitis and bronchiolitis’ admissions were highly associated with RSV.

For hospitalizations with ‘unspecified LRTI’ we estimated overall moderate proportions of hospitalizations associated with RSV (Figure 1E). Association with ‘unspecified LRTI’ was highest in age groups below 5 years across countries. Only in Denmark, no association to RSV was estimated in the age group 0-2 years (supplementary table 7).

The incidence rates of hospitalizations associated with RSV by diagnosis group varied considerably between countries (Supplementary Tables 4 to 7). The estimated incidence rates of hospitalizations with ‘bronchitis and bronchiolitis’ were high, especially in children under 3 years (supplementary table 6). A pattern of highest incidence rate in age group 0-2 months that dropped to less than 1 yearly hospitalization per 1000 in age group 3-4 years was seen in all countries (Figure 2D). In the other diagnostic groups, we found low yearly incidence rates per 1000 and in several age groups we found no association with RSV (Figure 2B,C,E).

Discussion

We found substantial proportions of admissions to hospital with respiratory infections associated with RSV in children younger than 3 years. Proportions in children younger than 12 months were especially high and a high proportion of admissions to hospital with ‘bronchitis and bronchiolitis’ were associated with RSV in children younger than 18 years. Comparing incidence rates of the 1-2 years age group and 85+ years showed a substantial burden of disease in the eldest age group as well as the young children. The diagnostic groups ‘pneumonia and influenza’ and ‘bronchitis and bronchiolitis’ had the highest proportions of admissions associated with RSV in age groups younger than 3 years.

When looking at the diagnosis specific hospitalizations we found discrepancies between countries. These country and age-specific discrepancies are likely due to differences in coding practices between countries.

All admissions to hospitals included in this study used ICD-10 coding, which may be subject to country or age specific coding practices. Differences in health care organizations and funding may also affect the hospital admitting practices. These differences in coding and admission practices are an important factor for our results but lies outside the scope of this analysis. To capture all respiratory diagnoses in our populations, we included all hospitalizations with mention of respiratory infection. Restriction to diagnoses listed in the first and second levels of diagnostic codes can lead to different estimates, especially in the elderly population [19]. We did however restrict to respiratory diagnostic codes, excluding diagnostics as sepsis or apnoea also common clinical presentations for RSV in infants. Without uniform coding practices, diagnosis group specific estimates are difficult to translate to other countries and cannot be generalized. Estimates of the RSV hospital burden across countries should therefore be based on overall respiratory hospital admissions or on uniform surveillance activities [20]. Our estimates are comparable to single region estimates based on similar methods, showing similar results though conducted in different age groups [17].

Our study has other limitations. In order to facilitate comparability between countries as much as possible, it was not possible to use age-specific laboratory confirmed RSV or influenza information. Our model therefore relies on national, aggregated laboratory-confirmed cases and is thus only informed by age-variation in the hospital admissions. Enhancing the models with reliable age-specific information of confirmatory tests would increase the validity of our estimates and perhaps partially reduce the between-country differences we observed that might have occurred due to diverging coding practices. *In the sensitivity analysis with age structured laboratory data we conducted with the Norwegian data we found that estimates were higher in age groups not often tested and lower among children under 5 years.* However, laboratory testing may suffer from similar diverging practices between countries as hospitalization codes, and age specific laboratory information may not be representative of actual circulation of pathogens within a given age group [8]. The laboratory results thus act as a minimum of virus circulation in the community at the time of testing. Where testing for RSV took place routinely or in tandem with testing for other pathogens, the laboratory confirmed positive tests are reflective of the dissemination of the pathogen. Further studies should be done comparing full time series alignment of both hospital admissions and laboratory confirmed cases to the approach we opted for here.

Second, we restricted the pathogens included in our analysis to influenza A and B and RSV. Other similar studies using time series models have included other pathogens such as rhinovirus, coronavirus, metapneumovirus and other respiratory viruses. Practices and clinical guidelines for requesting laboratory tests differ between countries. Addition of other respiratory pathogens may further increase the reliability of the time series model, if those pathogens are consistently tested for. This was not the case in the current study. Only Norway had reliable information on a larger range of respiratory pathogens from a local hospital setting—but since comparable data from other countries was lacking, those data have not been used here. Our model estimates may thus slightly overestimate the association with RSV. To adjust for some of this, cyclic trends were added to the model to capture the circulation of other pathogens not captured by RSV and influenza A and B. Other approaches for estimating the burden of RSV on respiratory hospitalizations exist, including other statistical approaches and building on preceding estimates including other pathogens, environmental variables and higher order harmonics, especially for the cyclic trends, and using splines in the analyzed data [19,21,22]. We chose a model approach based on simplicity, interpretability and translatability to existing estimates of country or age specific RSV burdens. When combining analyses from six countries, who simultaneously conducted model searches and data analysis, we found it preferable to limit the number of variables and restrict to a common distribution with a model commonly used, running the risk of missing out on models with higher support in the available data. However, our findings are in concordance with previous estimates as our modeled hospital admission rates on RSV for children younger than 1 year are between 14.7-90.4/1000. This range agrees with the previous estimates based on ICD-codes (41.3-112.0/1000) [4].

The utilization of time series of hospitalizations and laboratory confirmed infections benefits from not relying on RSV specific ICD-10. Compared to existing burden estimates we find corresponding tendencies with estimates of proportion of incidence elevated around 40-50% in most countries compared, possibly explained by deficiencies in RSV ICD-10 codes and testing [4].

Another major strength of this work is the cross-country collaboration on uniform definitions along with access to large health and population registers covering entire countries or regions. Each country contributed their local analysis to the study, building on national data from administrative registers and full population coverage that made sure that there were few issues with national representability of country-

specific results. The countries in the study are, however, exclusively Northern and Western European countries. Further research is called for to estimate the burden of RSV on hospitalizations in mid- east- and south Europe, as well as other world regions.

Conclusions

RSV constitutes a high burden on hospital admissions due to respiratory infections, with up to 60% of all respiratory infections presented at the hospital in young children being associated with RSV. While the burden diminishes with age, it seems to rise again in the elderly, highlighting the need for more attention to this group that may be particularly at risk for severe outcomes of respiratory infections. Our findings contribute to the overall understanding of RSV in hospitalizations. Future work may use these results as a basis for continent-wide disease burden estimates in Europe, as well as economic burden investigations to further contribute to knowledge of the burden of RSV on society and health care systems in Europe.

Footnote Page

Study Group Members

The RESCEU investigators are as follows:

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

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Conflict of Interests

AM, AT, CK, HB, LS, LF, MvB, MW, TL, XW, have no conflicts to declare outside the submitted work. HC declared that funding for the submitted work also supported meetings and travel. JP declared payments to institution from Sanofi, AstraZeneca and Fondation de France in other RSV projects. ST and MB are employees of Sanofi. TKF declared participating in research funded by Pfizer outside the submitted work. TH declared personal fees from Janssen outside the submitted work. YL reports grants from WHO and Wellcome Trust, outside the submitted work.

Approvals

Approval for this study was granted by the CPRD Independent Scientific Advisory Committee (reference number 15_260).

Approval for this study was granted by the Regional committees for medical and health research ethics - South-East A (reference number: 2017/1250)

According to Danish law, ethics approval is exempt for this research. Due to the nature of this research, there was no involvement of patients or members of the public in the design or reporting of this study. Direct dissemination to study participants is not possible. The publication only contains aggregated results and no personal data. The publication is therefore not covered by the European General Data Protection Regulation.

Disclaimer

Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

This work reflects only the author's views and opinions. The EC is not responsible for any use that may be made of the information it contains.

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Corresponding author

Caroline Klint Johannesen, Statens Serum Institut, Copenhagen Denmark. Email: cakj@ssi.dk, telephone: +45 2544 7557.

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Supplements:

Data Sources

Scotland:

The Scottish Morbidity Record (SMR01) is a national registry containing episode-based information on all inpatients and day cases at hospitals in Scotland. Currently diagnoses are recorded using International Classification of Diseases (ICD10) codes. Underlying medical conditions, defined by ICD-10 diagnosis codes in the primary diagnosis in hospital episodes within 5 years prior to the present admission, were recorded in the Scottish Morbidity Record. Children who were recorded to have any of these conditions during the observation time were considered as having the underlying medical conditions.

The Electronic Communication of Surveillance in Scotland (ECOSS) system captures laboratory results from all diagnostic and reference laboratories in Scotland. All positive RSV and influenza tests are included, though there is no denominator information on the tested population. Reliable data on RSV-positive confirmations were available from 2009 onwards and linked deterministically using a unique personal identifier (Community Health Index (CHI) number) to SMR01. For this study, data from SMR01 and ECOSS from 2010 to 2016 were included.

England

Clinical Practice Research Datalink (CPRD) is an ongoing primary care database of anonymized medical records from general practitioners. It is nationally representative of the UK population in terms of age, sex and ethnicity, and covers approximately 12.5% of the UK population. For this study, we used a subset of English practices who have consented to participate in the CPRD linkage scheme for the Hospital Episode Statistics (HES) Admitted Patient Care (APC) which provide secondary care inpatient and day case from National Health Service (NHS) hospitals in England. Each HES record contains a wide range of information about an individual patient admitted to an NHS hospital such as patient information (age, gender, ethnicity), administrative information (dates and methods of admission and discharge), and clinical information (about diagnoses and operations). Data on weekly laboratory confirmed cases of RSV and Influenzas A and B was compiled by the Public Health of England (PHE) within their ongoing surveillance of communicable diseases in England and made publicly available. For this study, we used data from 2007 to

2017, and estimated the weekly number of hospital admissions in the whole of England by extrapolating the weekly CPRD rates with mid-year England populations by age group.

The Netherlands

The Dutch Hospital Data (DHD) registration collects, manages, and processes hospital data, and manages standards for its registration. The data sources from DHD in the current study were LBZBASISTAB and LBZDIAGNOSENTAB of the years 2013 to 2017. All diagnoses were recorded using ICD10 classification. Perinatal data was provided by the Netherlands Institute Perinatal Registry of Obstetric care (www.perined.nl). The demographic database from Statistics Netherlands GBAPERSOONTAB was used to link data on gender and birth date to the admitted patients. This non-public microdata were provided by Statistics Netherlands (microdata@cbs.nl). For analysis we exported the data outside of the microdata services. For privacy issues, cells with 1-5 cases were reported as "≤5" during this procedure. Before analyses, we constructed a consolidated dataset in which the "≤5" cells were replaced with numbers between 1 and 5. Here we used the available total number of cases within each age stratum and case definition, such that total numbers of cases in the consolidated dataset matched the true totals. Virus diagnostic data were collected from 20 hospital and peripheral diagnostic laboratories spread throughout The Netherlands with help from the Dutch Working Group for Clinical Virology (NWKV).

Finland

The two primary data sources in the Finnish analysis are respiratory infection-related hospital admissions from the Finnish Care Register for Health Care (Hilmo) and laboratory-confirmed cases of RSV and influenzas A and B from the Finnish National Infectious Diseases Register (NIDR). Both Hilmo and NIDR are maintained by the Finnish Institute for Health and Welfare. As a continuation to Finnish Hospital Discharge Register, Hilmo contains detailed individual-level records on both inpatient care and other forms of specialized healthcare in hospitals nationwide from 1994 onwards. Inpatient care records between 2006 to 2016 from Hilmo were used to both identify the outcomes of interest and to define the at-risk population among the under 18-year-olds. General population records published by Statistics Finland were used to calculate incidence rates.

Norway

The Norwegian Patient Registry (NPR) holds individual level data from all hospitals in Norway since 2008. Information available on this registry include the personal identification number for each Norwegian citizen, demographic information, administrative data (dates of hospitalization and discharge), diagnostic data (International Classification of Diseases: ICD-10 codes) and reimbursement information [23].

Patients under 18 years of age identified in the NPR were linked to the Medical Birth Registry (MBR) to account for risk factors that may have not been recorded in their hospital records. Data on laboratory confirmed cases of RSV and Influenzas A and B were provided by Ullevål University Hospital in Oslo. We used the yearly hospital's catchment population and a rolling 3-week average to infer the numbers to the national level. The Norwegian data spans from week 27 in 2008 until week 26 in 2017.

Denmark:

Hospital admissions are contained in the Danish National Patient Registry (DNPR), which provides nationwide longitudinal registration of detailed administrative and clinical data and contains data an all hospital admissions since 1977. Patients identified with a respiratory infection in DNPR were linked to the Civil Registration System (CRS) to obtain additional information. The CRS contains basic personal information for all inhabitants with a registry number. We also utilized the Medical Birth Registry (MBR) to identify risk factors among patients under age 18 identified in DNPR. Data on weekly laboratory confirmed cases of RSV and Influenzas A and B was compiled by Statens Serum Institut (SSI) within their ongoing surveillance of communicable diseases in Denmark and made publicly available. The Danish data covers the years 2010-2017.

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Table and figure headings

Figures and tables to be found in separate document

Table 1. Average yearly admissions to hospital with respiratory infection associated with RSV in Scotland,

Figure 1. Age group specific proportions of hospitalizations associated with RSV within diagnostic groups (%). A) all hospitalizations with respiratory infections, B) hospitalizations with AURTI, C) hospitalizations with pneumonia and influenza, D) hospitalizations with bronchitis and bronchiolitis, E) hospitalizations with unspecified lower respiratory infection

Figure 2. Age group specific incidence rates of hospitalizations associated with RSV per year per 1000. A) all hospitalizations with respiratory infections, B) hospitalizations with AURTI, C) hospitalizations with pneumonia and influenza, D) hospitalizations with bronchitis and bronchiolitis, E) hospitalizations with unspecified lower respiratory infection

Supplementary tables and figures

Supplementary Table 2. Availability of hospitalization data and weekly data on pathogens

Supplementary Table 3. Diagnosis codes used to identify relevant respiratory diagnosis group

Supplementary Table 4. Average yearly hospital admissions with AURTI associated with RSV

Supplementary Table 5. Average yearly hospital admissions with pneumonia and influenza associated with RSV

Supplementary Table 6. Average yearly hospital admissions with bronchitis and bronchiolitis associated with RSV

Supplementary Table 7. Average yearly hospital admissions with unspecified LRTI associated with RSV

Supplementary Table 8. Average yearly hospital admissions with respiratory infections associated with RSV in children with high-risk factors (Gestational age <37 weeks, Cystic fibrosis, Congenital Heart Disease, Broncho-pulmonary dysplasia, or Downs syndrome).

Supplementary Table 9. RSV associated hospitalizations in Norway with age structured laboratory results as variable in models

Supplement figures

Supplementary Figures 2. Age distribution in tests Finland, Norway and Denmark

Supplementary Figures 3. Estimated weekly number of hospitalizations with respiratory infections associated with RSV in age groups 0-2 months, 3-5 months, 6-11 months, 1-2 years, and 3-4 years in Scotland, England, Netherlands, Finland Norway, and Demark.

Supplementary Figures 4. Estimated weekly number of hospitalizations with respiratory infections associated with RSV in age groups 5-17 years, 18-64 years, 65-74 years,75-84 years, and 85+ years in Scotland, England, Netherlands, Finland, and Demark.