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SUPPLEMENT ARTICLE

Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets

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Background. Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infection (RTI) in young children. Registries provide opportunities to explore RSV epidemiology and burden.

Methods. We explored routinely collected hospital data on RSV in children aged < 5 years in 7 European countries. We compare RSV-associated admission rates, age, seasonality, and time trends between countries.

Results. We found similar age distributions of RSV-associated hospital admissions in each country, with the highest burden in children < 1 years old and peak at age 1 month. Average annual rates of RTI admission were 41.3–112.0 per 1000 children aged < 1 year and 8.6–22.3 per 1000 children aged < 1 year. In children aged < 5 years, 57%–72% of RTI admissions with specified causal pathogen were coded as RSV, with 62%–87% of pathogen-coded admissions in children < 1 year coded as RSV.

Conclusions. Our results demonstrate the benefits and limitations of using linked routinely collected data to explore epidemiology and burden of RSV. Our future work will use these data to generate estimates of RSV burden using time-series modelling methodology, to inform policymaking and regulatory decisions regarding RSV immunization strategy and monitor the impact of future vaccines.

Keywords. respiratory syncytial virus; RSV; hospital admissions; national registry data; Europe.

Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infection (RTI) in infants and young children across the globe. Global estimates from 2015 suggest that approximately 33.1 million episodes of RSV-associated lower respiratory tract infection (LRTI) result in approximately 3.2 million hospital admissions among children younger than 5 years [1]. There are known risk factors for severe disease caused by RSV—such as prematurity, bronchopulmonary dysplasia, and congenital heart disease [2]. However, the majority of children hospitalized with RSV-associated disease are previously healthy, with no clinical risk factors for severe disease [3].

RSV is considered one of the world's greatest unmet vaccine needs [4]. Substantial effort is being put towards RSV disease prevention, with over 20 vaccine and monoclonal antibody candidates in phase 1–3 clinical trials as of late 2019 [5, 6]. Reliable country-specific RSV disease burden estimates are essential for most countries to inform policy making and regulatory decisions regarding novel RSV vaccines and other preventative strategies [7]. Of particular importance are age-specific estimates of RSV disease burden, in order to determine optimal target age(s) for interventions [7].

In many European countries, health systems routinely generate and collect very large amounts of patient-level data, including information on health care service utilization in the form of electronic health records. These routinely collected data are mostly used for monitoring national (or regional) spending on health care, medicine use, and functioning of the health care system [8]. In some countries, these data are available for secondary use for research purposes, primarily for those active in public health and research institutions [8]. However, these routinely collected datasets are underutilized for studies of RSV epidemiology and burden; many published studies instead focus on data at subregional or single-hospital level [9]. These national and regional registries provide unique and important opportunities to explore RSV epidemiology and burden to generate baseline evidence that can be used to inform national RSV immunization strategy and monitor the impact of a future vaccine over time.

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Our study explored national and regional routinely collected hospital data on RSV in children younger than 5 years in 7 countries in the European Union (EU)/European Economic Area (EEA), including linked hospital and laboratory data in 2 countries. We compared RSV-associated admission rates, seasonality, and time trends between countries, as well as the distribution of admissions by age in years and months.

METHODS

Study Design

We retrospectively studied RTI hospital admissions, RSV-coded admissions, and laboratory-confirmed RSV-associated admissions using routinely collected hospital admissions databases in 7 countries in the EU/EEA. We employed comparable data cleaning algorithms, definitions, and analysis to optimize comparability of results between countries.

National Registries

Full details of the national and regional registries used in this study are detailed in the Supplementary Material. We used national hospital registries containing individual-level patient data on all hospital admissions for Scotland, Denmark, Finland, the Netherlands, and Norway. We used the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) to extract these data for a representative sample from England, and regional hospital admissions data for the Veneto Region, Italy.

Study Populations

Supplementary Table 1 summarizes the hospital admission data extracts available for this study. We extracted all hospital admissions in children < 5 years of age (at date of admission) with any mention of RTI from each registry using International Classification of Diseases (ICD-9-CM or ICD-10) diagnosis codes (for full code lists see Supplementary Table 2). We analyzed admissions with any mention of RTI (hereby referred to as RTI admissions), RTI admissions with any mention of a pathogen-specific diagnosis code (pathogen-coded admissions), and RTI admissions with an RSV diagnosis code (RSV-coded admissions). The exception to this was the data from Italy, where pathogen-coded admissions were not available (only RSV-coded admissions). The time period of data availability differed by country, ranging from 16 years in Finland and Denmark to 4 years in the Netherlands (Supplementary Table 1).

We analyzed RTI admissions with a linked RSV-positive laboratory test (RSV-confirmed admissions) in Scotland and Finland, where linkages to national laboratory surveillance data were available. A hospital admission with a linked RSV-positive laboratory or point-of-care test was classified as RSV-confirmed if the laboratory record was within −7 to +2 days of the beginning of the admission. For Scotland, exact dates of admission were not available, so admissions were classified as RSV-confirmed if the laboratory record was within the same calendar week, or within 2 days of the beginning or end of the calendar week, of admission.

In all countries, acute inpatient and day cases were included. Routine/scheduled admissions were excluded. Transfers from 1 hospital to another were included as the same admission, as were any readmissions on the same day as discharge. Visits to emergency departments were not included if they did not result in admission.

Data Analysis

The total number of RTI, pathogen-coded, RSV-coded, and RSV-confirmed admissions in the extracts from each country were summarized by International Organization for Standardization (ISO) calendar week, year, age, diagnosis, and sex. Annual data were calculated as the period beginning ISO calendar week 27 and ending week 26 of the following year. For example, the 2001/2002 year begins during week 27 of 2001 and ends during week 26 of 2002.

Admissions were described by diagnosis group: upper respiratory tract infection (URTI), pneumonia and influenza, bronchiolitis and bronchitis, or unspecified LRTI (Supplementary Table 2). Admissions with 2 or more of these diagnosis group codes were included in a separate diagnosis group (2 + diagnosis group).

Age was analyzed by < 1 year and 1–4 years, and by month for children < 1 year old. For Denmark, Finland, Norway, and Scotland, calculation of age in months was based on the exact difference between day of admission and day of birth. For England and Italy, day of birth was imputed as the 15th of the month, to estimate age in months. For the Netherlands, exact day of birth was known for 96% of cases; for the remaining 4% of cases, day of birth was imputed as the 15th of the month. Any negative ages resulting from this imputation in very young infants were set to 0 months.

Admission rates were calculated for children age < 1 year and 1–4 years for each country. Admission rates were calculated using 1 January population (the Netherlands, Denmark, Norway, and Finland) or midyear population (Scotland and England) stratified by age. For midyear estimates, the average midyear population figures for 2001 and 2002 were used as the denominator for the 2001/2002 epidemiological year, etc. For the Veneto Region, Italy, exact population denominators were calculated from the catchment population. To extrapolate CPRD rates to the whole of England, rates per 1000 person-years were calculated as 1000 × (annual number of events) ÷ (annual number of total enrolled person-years in the CPRD database). Person-years is the sum of total years contributed by all acceptable patients from up-to-standard CPRD practices and eligible for linkage to hospital episode statistics data, allowing to take into account the different lengths of time the patients were followed. Estimation of the numbers of admissions in England was

then a direct extrapolation of rates with the midyear England populations by age group [10].

RESULTS

Summary of Results

Average annual RTI admission rates ranged from 81.2 to 112.0 per 1000 children aged < 1 year in Scotland, England, Finland, Norway, and Denmark (Figure 1). Lower rates were seen in Italy and the Netherlands: 41.3 and 42.0 per 1000 children aged < 1 year, respectively (Figure 1). Rates were lower for children aged 1–4 years in all countries.

Average annual RSV-coded admission rates ranged from 20.5 to 22.3 per 1000 children aged < 1 year in Scotland, Finland, Norway, and Denmark, whereas in children aged 1–4 years rates ranged from 1.25 to 2.24 per 1000 children (Figure 1). Average annual RSV-coded admission rates ranged from 8.6 to 11.7 per 1000 children aged < 1 year in England, the Netherlands, and Italy, whereas in children aged 1–4 years rates ranged from 0.2 to 0.3 per 1000 children.

Biennial peaks were seen in RSV-coded admission rates for Finland, Norway, and Denmark, with a higher admission rate one year followed by a lower rate the next (Figure 1).

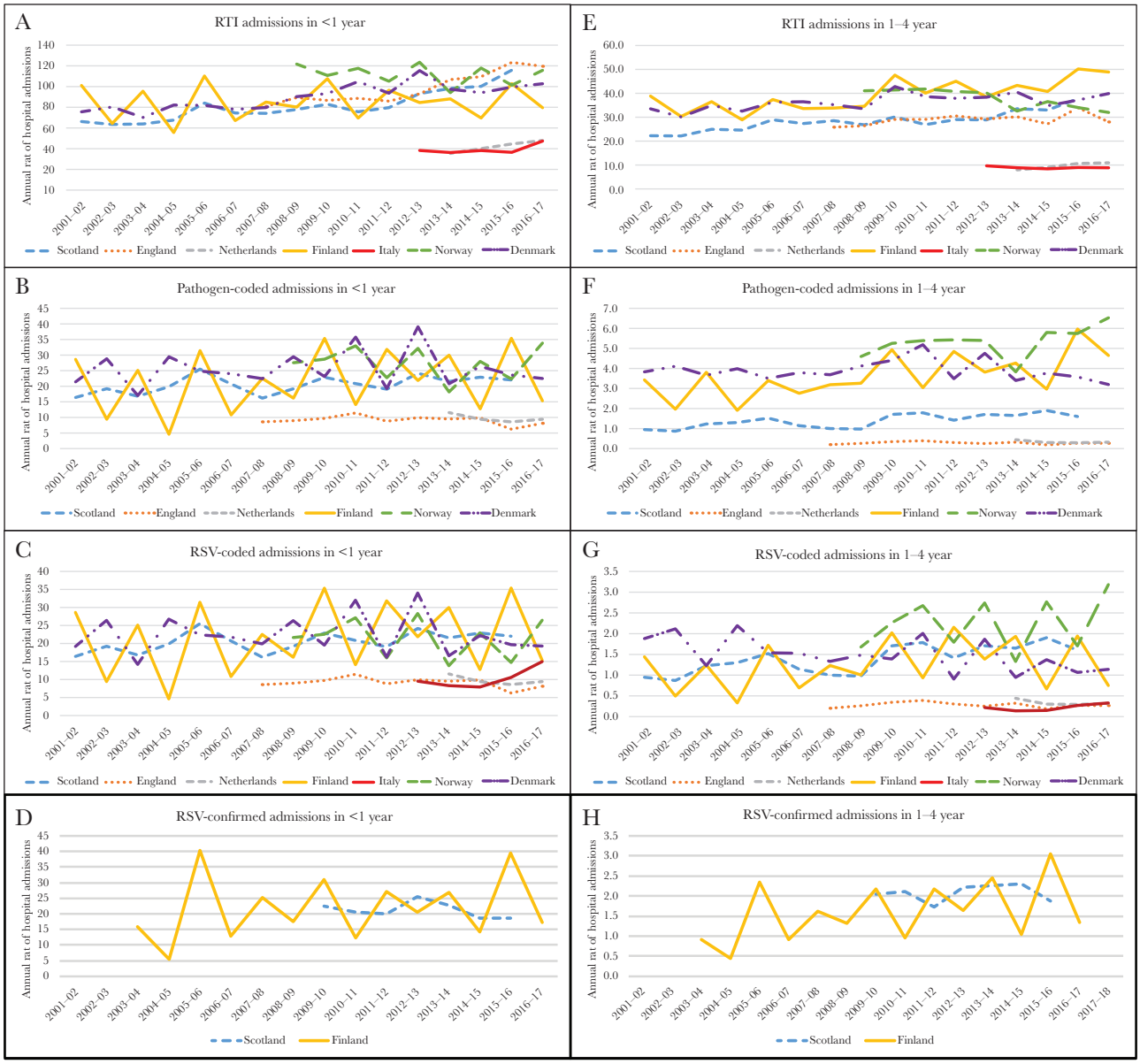

Figure 1. *A–H*, Annual hospital admission rates for all respiratory tract infection admissions, pathogen-coded admissions, respiratory syncytial virus (RSV)-coded admissions, and RSV-confirmed admissions in < 1 year olds and 1–4 year olds.

Annual average RSV-confirmed admission rates were 21.2 per 1000 children < 1 year in Scotland and 21.9 per 1000 children < 1 year in Finland. For children aged 1–4 years, RSV confirmed admission rates were 1.6 per 1000 in Finland and 2.1 per 1000 in Scotland.

Supplementary Table 3 describes the average annual number of RTI admissions, pathogen-coded admissions, and RSV-coded admissions in each country during the study period, by patient characteristics. In every country there was a higher number of RTI admissions in male compared to female children (M:F ratio 1.26–1.66). The percentage of RTI admissions with any pathogen-specific diagnosis code ranged from 16% (Finland) to 23% (the Netherlands), with the exception of England which had the lowest percentage of pathogen-coded admissions at 7% (Supplementary Table 3 and Supplementary Figure 1). The percentage of pathogen-coded admissions was highest in children < 3 months old in all countries.

The percentage of RTI admissions with an RSV code ranged from 11% (Norway and Finland) to 15% (Italy), again with the exception of England which had the lowest percentage of RSV-coded RTI admissions at 5%. However, the percentage of pathogen-coded admissions that were RSV-coded ranged from 57% to 72% in all children < 5 years. The percentage of pathogen-coded admissions that were RSV-coded was highest in children < 1 year: 62% in Scotland, 73% in the Netherlands, 77% in Norway, 85% in England, 86% in Finland, and 87% in Denmark (Supplementary Figure 1). In children aged 1–4 years, the percentage of pathogen-coded admissions that were RSV-coded ranged from 15% in the Netherlands to 39% in Norway (Supplementary Figure 1).

In Scotland and Finland, 40% and 45% of RTI admissions in children aged < 3 months had a linked RSV-positive test, compared to 31% and 29% of children aged 3–5 months, 17% and 12% of children aged 6–11 months, and 8% and 4% of children aged 1–4 years, respectively (Supplementary Table 4). In Scotland, 46% of bronchiolitis and bronchitis admissions had a linked RSV-positive test compared to 19% in Finland. In both Scotland and Finland, the number of RSV-confirmed admissions with a diagnosis of URTI was considerably higher than the number of RSV-coded admissions with a diagnosis of URTI. The proportion of RSV-confirmed admissions with an RSV diagnosis code was 73% in Scotland and 70% in Finland.

Seasonality of Admissions

Supplementary Figure 2 shows the weekly number of RTI and RSV-coded RTI admissions in children < 5 years, per country. The clear pattern of RSV-coded admissions, peaking in the winter months, is shown. In some countries—particularly Finland, Norway, and Denmark—RSV-coded admissions had more variation in seasonality, with some years showing 2 peaks in admissions within the same RSV season. Finland showed the greatest variation in seasonality of RSV-coded admissions each year compared to the other countries.

Admissions by Age

In all countries, the number of RSV-coded RTI admissions was significantly higher in children aged < 1 years compared to those aged 1–4 years, and decreased with increasing age (Supplementary Figure 3). Of the RSV-coded admissions, 70%–92% were in children aged < 1 year.

Patterns in RSV-coded admissions by month of age for children aged < 1 year were markedly similar in all countries (Supplementary Figure 4). RSV-coded admissions peaked in children aged 1 month in all countries. The percentage of RSV-coded admissions in children < 1 year that were in those aged 1 month ranged from 13% in Norway to 27% in Italy. RSV-coded admissions then decreased with increasing age after 1 month in all countries.

DISCUSSION

In this study, we demonstrate the use of routinely collected data to explore the epidemiology and burden of RSV in 7 European countries. We found similar patterns in RSV-associated hospital admissions by age in each country, with the highest burden in children < 1 year old and a peak in children aged 1 month. Average annual rates of RTI admission ranged from 41.3 to 112.0 per 1000 children aged < 1 year, and RSV-coded admission rates ranged from 8.6 to 22.3 per 1000 children aged < 1 year. In children aged < 5 years, 57%–72% of RTI admissions with a specified causal pathogen were coded as being due to RSV, with 62%–87% of pathogen-coded admissions in children < 1 year coded as being due to RSV. Biennial patterns were seen in RSV-coded admission rates in Finland, Norway, and Denmark. Total counts, age distribution, and seasonality of RSV-coded and RSV-confirmed admissions were similar, in both Scotland and Finland, and 70%–73% of RSV-confirmed admissions had an RSV diagnosis code.

The differences in hospital admission rates between countries is in line with a global study exploring hospitalization rates of RSV-associated ALRI [11]. The rates of RSV-coded admissions calculated in our study are similar to previous country-specific estimates of RSV-associated admissions. For example, a previous study in Scotland estimated an RSV-associated admission rate of 21.9 per 1000 infants, whereas our study calculated an RSV-confirmed admission rate of 21.2 per 1000 infants [12]. Both of these estimates are likely to be an underestimate of the true burden of RSV in secondary care, as it is estimated that RSV-associated admission rates could be as high as 35.1 per 1000 infants in the UK [13]. In Denmark, a previous study estimated 29.4 RSV-associated admissions per 1000 infants from 2010 to 2015 [9], whereas our study found 22.3 RSV-coded admissions per 1000 infants. In the Netherlands, previous studies have estimated RSV-associated admission rates of 8.4, 10, and

12 per 1000 (mainly or only full-term) infants, or 40.5 per 1000 late-preterm infants (33–35 weeks gestational age); while the latter estimate is much higher than our estimate of 9.7 RSV-coded admissions per 1000 infants, we have not stratified by gestational age in our study [14–17]. The differences between rates of admission between countries could be attributed to differences in health care systems, coding practices, testing practices, or the circulation of RSV. We found that Denmark, Finland, and Norway had very similar rates of RTI admissions, pathogen-coded admissions, and RSV-coded admissions. Italy and the Netherlands had very similar—and much lower—rates of RTI and RSV-coded RTI admissions. This could reflect the similarity in health care systems in the Nordic countries [18], as well as similarities and differences in coding and testing practices. For example, Scotland and England had very similar rates of RTI admissions, but England had much lower rates of pathogen-coded admissions. This is likely to reflect differences between National Health Service (NHS) Scotland and NHS England, including differences in diagnosis coding practices; lack of coding of causal pathogens within English hospital admissions data has previously been noted [11, 13].

Acknowledging the important role of coding practices in the coding of RSV within admission registries, we analyzed RTI admissions with any pathogen-specific diagnosis code to identify differences in coding practices that could account for differences in RSV-coded admission rates. The percentage of RTI admissions with any pathogen-specific code ranged from 7% in England to 23% in the Netherlands; a large proportion of RTI admissions therefore having no causal pathogen coded. When considering pathogen-coded admissions only, overall, 57%–72% were coded as being due to RSV; this was higher in children < 1 year (62%–87%). These differences in coding could reflect differences in testing practices, which we were unable to assess in this study due to lack of availability of testing denominator data, as well as bias in coding of RSV towards younger infants.

Average annual RSV-coded admission rates ranged from 9.5 to 50 times higher in children aged < 1 year compared to children aged 1–4 years in each country. It is widely recognized that RSV has a high burden in children < 1 year old, and that young infants are therefore a key target population for interventions [1]. This pattern was seen in RSV-coded and RSV-confirmed admissions in our study. As we did not have access to laboratory confirmed RSV-negative cases, biases in testing towards younger infants could not be investigated. Nevertheless, the high burden in infants < 3 months old, peaking in children aged 1 months, has also been demonstrated by previous studies and highlights the need to protect these very young infants through targeted interventions [9, 19, 20].

Rapid identification of viral respiratory pathogens is increasingly important in determining treatment with antibiotics and in implementing pathogen-specific infection control measures [21, 22]. There were similarities in total counts, seasonality, and age distribution of RSV-coded and RSV-confirmed admissions in both Scotland and Finland. This suggests that, depending on the research objectives, RSV-coded admissions could be used as a proxy for RSV-confirmed admissions in RSV burden studies using national datasets where laboratory data are not available, saving time and resources compared to data linkage studies using national laboratory surveillance data or prospective data collection [23]. A recent study in Germany also found that RSV-specific ICD-10 codes may be a useful indicator to describe RSV epidemiology, though they underestimate the actual number of RSV infections [24]. However, our conclusions for Scotland and Finland cannot be extrapolated to other countries, due to the differences in coding and testing practices by country. Furthermore, increased use of point-of-care testing for respiratory viruses may change the landscape of respiratory virus surveillance and diagnostic coding in the future.

Our results demonstrate the benefits and limitations of using linked routinely collected data to explore the epidemiology and burden of RSV. The main benefits for this type of research are the national representativeness of the data sources, enabling trends and patterns to be monitored over time, supporting service planning and providing data to inform and evaluate government policy. For research purposes, the poor coding practices, limited understanding of RSV testing practice, and lack of availability of testing data in many countries, limits the interpretation of the rate and patterns of RSV-coded admissions. Nevertheless, our study finds the same seasonality and age patterns compared to other studies within these countries, highlighting the high burden in children aged < 1 year and the peak in infants aged 1 month. Our future work will use these data to generate estimates of the true burden of RSV in secondary care using time-series modelling methodology, contributing to baseline evidence on RSV epidemiology and burden that can be used to inform policymaking and regulatory decisions regarding national RSV immunization strategy, and monitor the impact of a future vaccine over time.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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