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Respiratory syncytial virus-associated hospital admissions and bed days in children under 5 years in 7 European countries

Running title: respiratory syncytial virus in Europe

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Abstract

Background

Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infections (RTI) in young children. High-quality country-specific estimates of bed days and length of stay (LOS) show the direct and indirect burden of RSV-RTI on secondary care services, and can be used to inform RSV immunisation implementation decisions.

Methods

We estimated the hospital burden of RSV-associated RTI (RSV-RTI) in children under 5 years in 7 European countries (Finland, Denmark, Norway, Scotland, England, the Netherlands and Italy) using routinely collected hospital databases during 2001-2018. We described RSV-RTI admission rates during the first year of life by birth month and assessed their correlation with RSV seasonality in 5 of the countries (except for England and Italy). We estimated average annual numbers and rates of bed days for RSV-RTI and other-pathogen-RTI, as well as the hospital LOS.

Results

We found that infants born 2 months before the peak month of RSV epidemics more frequently had the highest RSV-RTI hospital admission rate . RSV-RTI hospital episodes accounted for 9.9 to 21.2 bed days per 1,000 children under 5 years annually, with the median (interquartile range; IQR) LOS ranging from 2 days (0.5-4 days) to 4 days (2-6 days) between countries. Between 70% and 89% of these bed days were in infants <1 year, representing 40.3 (95% CI 40.1-40.4) -91.2 (95% CI 90.6-91.8) bed days per 1,000 infants annually. The number of bed days for RSV-RTI was higher than that for RTI associated with other pathogens in infants <1 year, especially in those <6 months.

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Discussion

RSV disease prevention therapies (monoclonal antibodies and maternal vaccines) for infants could help prevent a substantial number of bed days due to RSV-RTI. “High-risk” birth months should be considered when developing RSV immunisation schedules. Viariation in LOS between countries might reflect differences in hospital care practices.

Key words: respiratory syncytial virus; hospital admission; bed days; birth month; Europe.

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Introduction

Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infections (RTI) in young children, causing an estimated 3.2 million hospital admissions and 118,000 deaths in children under 5 years globally in 2015 [1]. Currently, treatments for RSV are mainly supportive and there is no vaccine for RSV yet, though a monoclonal antibody (palivizumab) is currently available for use in high-risk children to prevent severe RSV infection [2, 3]. A number of RSV vaccine and monoclonal antibody candidates are being developed. In the recent phase 3 trial, the effect of a RSV F maternal vaccine did not meet the primary endpoint, but showed the efficacy of 44% against the additional endpoint - RSV-associated RTI hospitalisation [4]. Two other maternal vaccines and one monoclonal antibody targeting the paediatric population are currently under assessment in phase 3 trials [2, 4-6]. Given the recent progress in the development of RSV interventions, high-quality country-specific burden estimates are warranted to inform national RSV intervention implementation strategies in a timely manner. We have previously shown that average annual RSV-RTI admission rates ranged from 8.6 to 22.3 per 1,000 children aged <1 year in 7 European countries, and ranged from 0.3-2.1 per 1,000 children aged 1-4 years [7]. In this analysis, we build on the previous work to further estimate the number and rate of bed days and length of stay (LOS) for RSV-RTI admission in the selected European countries and the risk factors for prolonged hospital stay at RSV-RTI admission [8]. The estimates of bed days and LOS demonstrate the direct and indirect burden of RSV-RTI on country secondary care services respectively, and show the disease severity of RSV-RTI in risk groups. Estimates of bed days can be used directly in cost-effectiveness analysis to evaluate new interventions and intervention strategies [9].

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It is well known that infants have the highest RSV infection rate. In addition to young age, the timing of birth is also shown to be associated with risk of RSV infection in the first year of life [10-16]. This is possibly because infants born in different time of a year are at different ages during the RSV epidemic, and age is a key factor influencing the risk of severe RSV infection [7]. In the European setting [10, 11, 13, 16], most of the previous studies on the association between timing of birth and RSV infection rates were small in size, had short observation periods (2-4 years) and did not report nationally representative data. In this report we describe RSV-RTI admission rates by birth month during the first year of life using national hospital databases available in 5 European countries and assess how it is related to the RSV seasonal series in time with the aim of providing data to inform future RSV immunisation schedule optimization.

Methods

Study design and data sources

The study design and data sources have been described previously [7]. Briefly, we conducted a retrospective study of overall RTI hospital admissions (i.e., RTI with or without an associated pathogen), RSV-RTI admissions, and other pathogen-RTI admissions in children under 5 years of age using routinely collected hospital admissions databases in 7 countries in the European Union/European Economic Area (appendix Table S1). We used national hospital registries for Scotland (2001-2016), Denmark (2001-2017), Finland (2001-2017), the Netherlands (2013-2017), and Norway (2008-2017). For England, we used Clinical Practice Research Datalink linked to Hospital Episode Statistics (2007-2017). We used subnational hospital admissions data for

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the Veneto Region of Italy (2012-2018), with an estimated average population of about 226,800 children under 5 years per year (accounting for about 9% of the children under 5 years in Italy). As used in our previous paper [7], we defined RSV-RTI and other-pathogen-RTI admissions based on International Classification of Diseases (ICD-9-CM or ICD-10) diagnosis codes (for full code lists see appendix Table S2). RTI admission was defined as an admission with any mention of RTI in the diagnosis codes. RSV-RTI admission was an RTI admission with any mention of a RSV diagnosis code; other-pathogen-RTI admission was an RTI admission with any mention of a pathogen-specific diagnosis code. For the Veneto Region of Italy, we only presented data on RSV-RTI as data on other-pathogen-RTI were unavailable.

Statistical analysis

We estimated RSV-RTI admission rates in the first year of life by birth month in Scotland, Denmark, Finland, the Netherlands and Norway. For this analysis, the numerator was the number of RSV-RTI admissions during the first year of life in infants born in each month, and the denominator was the number of live births per month (thus refered as “birth cohort” series) [17-20]. We assessed the cross-correlation between the “birth cohort” series and the RSV seasonal series in each country at time lags from -5 months to 5 months using the Pearson’s correlation. The RSV seasonal series was shown using the annualised RSV-RTI hospital admission rates by calendar month.

We estimated the average annual number of bed days in children under 5 years for RSV-RTI and other-pathogen-RTI in the countries where data were available. The number of bed days was assumed 0.5 days when the admission and discharge were on the same day. Where available, overnight hospital stay <24 hours was considered to be equivalent to 1 bed day as its cost is

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higher than a day case. After accounting for country population statistics [7], we reported average annual rate of bed days per 1,000 population in children under 5 years, and in infants <1 year and children aged 1-4 years. We described the distribution of bed days due to RSV-RTI and other-pathogen-RTI by narrow age bands (<3 months, 3-5 months, 6-11 months, and 1-4 years of age) and by the presence of underlying medical conditions that were defined by ICD diagnosis codes (any of prematurity, bronchopulmonary dysplasia, cystic fibrosis, and congenital heart disease) versus the distribution of the number of hospital episodes [7, 8]. For each RSV-RTI hospital episode (and other-pathogen-RTI), we calculated the number of bed days as the length of stay (LOS) in days among children under 5 years in each country. We reported the median LOS for RSV-RTI and other-pathogen-RTI, and the distribution of hospital episodes by fine LOS groups (<1 day, 1-day interval between 1 and 7 days, 8-14 days, 15-29 days, and 30+ days) for RSV-RTI and other-pathogen-RTI, separately.

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Results

Birth month

In Finland, infants who were born in December and January most frequently had the highest RSV-RTI admission rates in the first year of life compared to other birth months (Figure 1); the lowest rates were most frequently found in those born in June (appendix Table S3). In Denmark and Norway, infants who were born in December most frequently had the highest RSV-RTI admission rates in the first year of life, and the lowest rates were most frequently found in those born in May. In Scotland, infants who were born in November most frequently had the highest RSV-RTI admission rates; the lowest rates were most frequently found among infants born in March. In the Netherlands, the highest RSV-RTI admission rates were observed in infants who were born in October-December, and the lowest rates were in those born in March and April.

We found the strongest positive correlation when moving the RSV seasonality series ahead by 2 months relative to the birth cohort series, with the Pearson's correlation coefficients ranging from 0.64 (95%CI 0.55-0.72) in Denmark to 0.91 (95%CI 0.83-0.95) in the Netherlands. We found the strongest negative correlation when lagging the RSV seasonality series by 3 months relative to the birth month series in the countries except for Norway (4 months for Norway), and the Pearson's correlation coefficients ranged from -0.45 (95%CI -0.56 to -0.33) in Finland to -0.66 (95%CI -0.82 to -0.40) in the Netherlands(detailed Pearson's correlation coefficients in appendix Figure S1). In line with Figure 1, the correlation coefficients suggested that infants born 2 months before the peak month of RSV admissions were more likely to have the highest

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RSV-RTI admission rates during the first year of life, and infants born 3-4 months after the peak month tended to have the lowest RSV-RTI admission rates during the first year of life (appendix Figure S1). The median ratio between the highest rates and lowest rates ranged from 3.2 (IQR, 2.8-3.6) in Scotland to 10.2 (IQR, 4.4-17.6) in Finland.

Bed days for RSV-RTI and other-pathogen-RTI

RSV-RTI caused between 4,131 and 34,996 bed days annually in Scotland, England, the Netherlands, Finland, Denmark, and Norway, and 2,817 bed days annually in the Veneto Region of Italy (appendix Table S4). Between 70% (Norway) and 89% (the Netherlands) of these bed days were in infants <1 year. After accounting for country population statistics, RSV-RTI were associated with 9.9 (95% CI 9.8-10.0) to 21.2 (21.1-21.3) bed days per 1,000 children under 5 years annually, 40.3 (40.1-40.4) to 91.2 (90.6-91.8) bed days per 1,000 infants aged <1 year annually, and 1.1 (1.0-1.1) to 7.1 (7.0-7.2) per 1,000 children aged 1-4 years annually (appendix Table S4). Compared to other-pathogen-RTI admission, the annual number of bed days for RSV-RTI admission was 1.5-3.5 times higher in children under 5 years across the countries (appendix Table S5). By narrower age bands, the annual average number of bed days for RSV-RTI was 2.8-7.9 times higher than other-pathogen-RTI in infants <3 months, 2.3-9.3 times higher for 3-5 months, 1.1-4.8 times higher for 6-11 months, while lower (0.4-0.9 times) for children aged 1-4 years (appendix Table S5).

Young infants and underlying medical conditions

In countries except for Italy, infants <3 months who were admitted with RSV-RTI had a disproportionate number of bed days compared to the number of hospital episodes (37-58% of bed days in children under 5 years versus 33-52% of hospital episodes) (appendix Table S5). In

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all the countries, children under 5 years with underlying medical conditions had a disproportionate number of bed days (5-47% of the bed days in children under 5 years versus 3-26% of the RSV-RTI hospital episodes). The longer hospital stay for young infants and children with underlying medical conditions was not RSV-specific, as similar patterns were also observed for other-pathogen-RTI (detailed results in Table S7-S8, Figure S3).

Length of hospital stay for RSV-RTI by country

The median number of LOS for RSV-RTI ranged from 2 days (IQR 0.5-4 days) in Finland to 4 days (IQR 2-6 days) in the Netherlands (appendix Table S6). Between 29% and 73% of RSV-RTI hospital episodes in the 7 countries had a LOS of 0-3 bed days, 22-52% for 4-7 bed days, 4-16% for 8-14 bed days, and 0.5-7% for ≥15 bed days. The proportion of RSV-RTI hospital episodes with a LOS of <1 day varied substantially between countries, with the lowest proportion in the Netherlands and the Veneto Region of Italy (<1%), and the highest proportion in Finland (31%). Additionally, the Veneto Region of Italy had a lower proportion of RSV-RTI hospital episodes with a LOS of 1-2 days and a higher proportion of RSV-RTI hospital episodes with a LOS of 4-7 days compared to the other countries. The Veneto Region of Italy and the Netherlands had a higher proportion of RSV-RTI hospital episodes with a LOS of 8-14 days than the other countries. After excluding the hospital admissions with a LOS of <1 day, the proportion of RSV-RTI hospital episodes with a LOS of 1 day was still lowest in the Veneto Region of Italy, followed by the Netherlands and the other countries.

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Discussion

In this study, we report the epidemiology and hospital burden of RSV-RTI in children under 5 years in 7 European countries using 6 national healthcare databases and one subnational database. Infants born 2 months (more frequently in November-January) before the peak month of RSV admissions were more likely to have the highest RSV-RTI admission rate during the first year of life. Infants <1 year had substantially higher rates of bed days compared to children aged 1-4 years, and accounted for 70-89% of the bed days in children under 5 years. The annual number of bed days for RSV-RTI was higher than other-pathogen-RTI in infants <1 year. Infants <3 months and children with underlying medical conditions had a disproportionate number of bed days for RTI associated with RSV and other pathogens compared to the number of hospital episodes.

Infants usually experience one RSV season, or part of two RSV seasons during their first year of life. However, because susceptibility to RSV infection can vary by month of age, infants born in different months relative to the local RSV season can have substantially different risks for RSV-RTI admission. The result that infants born 2 months before the peak of RSV admissions are more likely to have the highest rate is in line with our previous finding that the highest rates occur in infants who are 1-2 months of age [7]. Interestingly, serological studies [21, 22] found that infants born during winter, spring, and early summer had a similar risk of RSV infection at age <1 year, but those born after the first half of the RSV season had a higher level of maternally derived antibodies. The difference in the level of maternally derived antibodies may also be related to the different RSV-RTI hospital admission rates by birth month. In Europe, nationally generalizable results on the association between birth month and RSV-RTI

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admissions are only found in England [16]. Consistent with our result, the English study found that infants born in September-November during 2010-2014 had the highest odds (odds ratio of 2.1-2.4) of a positive RSV test during their first year of life compared to those born in January. Similar results were also found in two subnational studies in Spain and the Netherlands, as well as in a multi-center Spanish study [10, 11, 23]. In contrast, another Dutch study on patients in general practice found that being born during April-September was associated with higher odds of RSV lower respiratory tract infections compared to other periods [13]. The RSV-RTI general practice episodes peaked during November-December, about 1-2 months earlier than the peak of RSV hospital episodes we observed in the Netherlands. This may explain the shift of "high-risk" birth months [24, 25]. A Danish study did not find a significant association between birth timing (in season) and RSV-associated admissions, but this study was not adequately powered [26].

The country-specific estimates of bed days show the burden of RSV-RTI in children under 5 years on secondary care services. The average annual number of bed days due to RSV-RTI per 1,000 population was 10-65 times higher in infants <1 year than in children aged 1-4 years across the 7 countries, highlighting the substantial RSV-RTI burden among infants.

Our median estimates of LOS per episode are generally comparable to the average LOS for the European region (2.7 days; 95% CI: 2.6-2.7) estimated in a systematic review [27]. Differences in LOS between countries were observed, which may reflect differences in hospital care practices between countries. For example, the Netherlands and the Veneto Region of Italy had a higher median LOS at RSV-RTI admission than the other countries, mainly driven by the very small proportion of hospital episodes with <1 day of LOS in the two areas and the higher proportion

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of hospital episodes with 8-14 days of LOS. In the Netherlands only clinical admissions were included; not day admissions for observation. After removing the hospital episodes with a LOS of <1 day, the median LOS for RSV-RTI admission in the Netherlands (4 days) and the Veneto Region of Italy (4 days) was still higher than that of the other countries (3 days). Additionally, the hospital admission rate of RSV-RTI in these two areas was low [7]; it could be that the admission policy in these two areas is more strict than that in other countries. Compared to our incidence estimates [7], LOS seems to be negatively associated with RSV-RTI hospital admission rates in 5 countries except for Denmark and England.

Limitations of this study are similar to those in our previous study [7]. We used ICD codes to identify RSV-RTI admissions (and other-pathogen-RTI). We previously verified that the total counts and age distribution of RSV-coded admissions were comparable to that of RSV-confirmed admissions based on laboratory records in both Scotland and Finland [7]. Unfortunately, this verification cannot be extrapolated to other countries. Additionally, we were unable to assess bias in testing or under-detection due to the unavailability of laboratory-confirmed RSV-negative records. The lack of coding of causal pathogens for a large proportion of RTI admissions (between 7% in England and 23% in the Netherlands were pathogen-coded) [7] might suggest that we have underestimated the true number of bed days for RSV-RTI and other-pathogen-RTI. The association between birth month and RSV-RTI admission rates might be affected if differences in coding and viral testing practices exist between the RSV season and the rest of the year. Given the differences in coding and viral testing practices between countries, country-specific estimates might have been affected to varying degrees. Coding practices could have also changed over time. For example, the proportion of RTI hospital

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admissions with any pathogen-specific codes decreased in England and Scotland since 2013, and this indicates that estimates of bed days for the two nations could have been underestimated to a larger degree in the most recent years [7]. Our future work is to generate estimates of RSV hospital burden using the time-series modelling approach, which can reduce coding related biases. Hospital-acquired infections were not excluded in our analyses; estimates of bed days and LOS could have been biased due to the mis-attribution of hospital stays before acquiring the RSV infection, especially in children with underlying medical conditions. Since RSV burden could be influenced by climate, socioeconomic and other environmental factors [1], the estimates for Veneto Region of Italy may not be representative of the whole country. Additionally, the country population statistics used to estimate rates of bed days could also be biased due to errors in data collection (population registers and censuses) [28].Conclusions

This analysis of multi-year, nationally representative hospital databases in 7 European countries provides high-quality evidence to support country secondary care services planning and future decision making related to national RSV intervention strategies. The estimates provide evidence to support evaluation of RSV intervention programmes. RSV disease prevention therapies (monoclonal antibodies and maternal vaccines) given to infants could help prevent a substantial number of bed days due to RSV-RTI. Our results from the birth month analysis should inform future development of RSV immunisation schedules.

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Footnote page

Study Group Members

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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

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and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest

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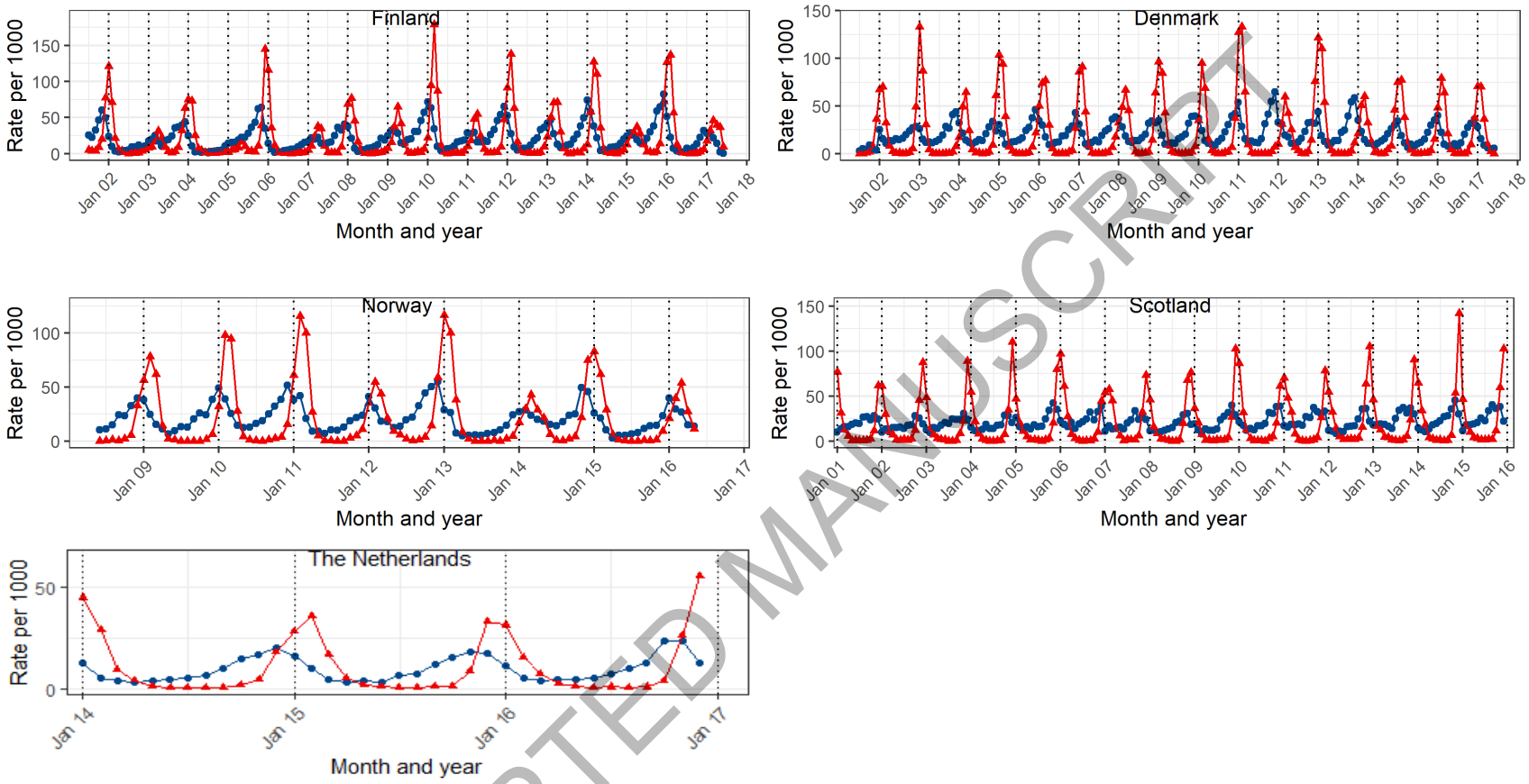

Figure 1. RSV-RTI admission rates per 1,000 infants <1 year by birth month and calendar month in Finland, Denmark, Norway, Scotland and the Netherlands.

Blue points are hospital admission rates of RSV-RTI per 1,000 live births by birth month; red points are annualised rates of RSV-RTI per 1,000 infants by calendar month. Dotted vertical lines denote January of each observation year.