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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. Variation in LOS between countries might reflect differences in hospital care practices.

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

Word count: [abstract 299](#); [main text 2760](#)

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1 Introduction

2 Respiratory syncytial virus (RSV) is a leading cause of respiratory tract infections (RTI) in young
3 children, causing an estimated 3.2 million hospital admissions and 118,000 deaths in children
4 under 5 years globally in 2015 [1]. Currently, treatments for RSV are mainly supportive and
5 there is no vaccine for RSV yet, though a monoclonal antibody (palivizumab) is currently
6 available for use in high-risk children to prevent severe RSV infection [2, 3]. A number of RSV
7 vaccine and monoclonal antibody candidates are being developed. In the recent phase 3 trial,
8 the effect of a RSV F maternal vaccine did not meet the primary endpoint, but showed the
9 efficacy of 44% against the additional endpoint - RSV-associated RTI hospitalisation [4]. Two
10 other maternal vaccines and one monoclonal antibody targeting the paediatric population are
11 currently under assessment in phase 3 trials [2, 4-6]. Given the recent progress in the
12 development of RSV interventions, high-quality country-specific burden estimates are
13 warranted to inform national RSV intervention implementation strategies in a timely manner.
14 We have previously shown that average annual RSV-RTI admission rates ranged from 8.6 to
15 22.3 per 1,000 children aged <1 year in 7 European countries, and ranged from 0.3-2.1 per
16 1,000 children aged 1-4 years [7]. In this analysis, we build on the previous work to further
17 estimate the number and rate of bed days and length of stay (LOS) for RSV-RTI admission in the
18 selected European countries and the risk factors for prolonged hospital stay at RSV-RTI
19 admission [8]. The estimates of bed days and LOS demonstrate the direct and indirect burden
20 of RSV-RTI on country secondary care services respectively, and show the disease severity of
21 RSV-RTI in risk groups. Estimates of bed days can be used directly in cost-effectiveness analysis
22 to evaluate new interventions and intervention strategies [9].

23 It is well known that infants have the highest RSV infection rate. In addition to young age, the
24 timing of birth is also shown to be associated with risk of RSV infection in the first year of life
25 [10-16]. This is possibly because infants born in different time of a year are at different ages
26 during the RSV epidemic, and age is a key factor influencing the risk of severe RSV infection [7].
27 In the European setting [10, 11, 13, 16], most of the previous studies on the association
28 between timing of birth and RSV infection rates were small in size, had short observation
29 periods (2-4 years) and did not report nationally representative data. In this report we describe
30 RSV-RTI admission rates by birth month during the first year of life using national hospital
31 databases available in 5 European countries and assess how it is related to the RSV seasonal
32 series in time with the aim of providing data to inform future RSV immunisation schedule
33 optimization.

34 [Methods](#)

35 Study design and data sources

36 The study design and data sources have been described previously [7]. Briefly, we conducted a
37 retrospective study of overall RTI hospital admissions (i.e., RTI with or without an associated
38 pathogen), RSV-RTI admissions, and other pathogen-RTI admissions in children under 5 years of
39 age using routinely collected hospital admissions databases in 7 countries in the European
40 Union/European Economic Area (appendix Table S1). We used national hospital registries for
41 Scotland (2001-2016), Denmark (2001-2017), Finland (2001-2017), the Netherlands (2013-
42 2017), and Norway (2008-2017). For England, we used Clinical Practice Research Datalink linked
43 to Hospital Episode Statistics (2007-2017). We used subnational hospital admissions data for

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

53 Statistical analysis

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

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

66 higher than a day case. After accounting for country population statistics [7], we reported
67 average annual rate of bed days per 1,000 population in children under 5 years, and in infants
68 <1 year and children aged 1-4 years. We described the distribution of bed days due to RSV-RTI
69 and other-pathogen-RTI by narrow age bands (<3 months, 3-5 months, 6-11 months, and 1-4
70 years of age) and by the presence of underlying medical conditions that were defined by ICD
71 diagnosis codes (any of prematurity, bronchopulmonary dysplasia, cystic fibrosis, and
72 congenital heart disease) versus the distribution of the number of hospital episodes [7, 8]. For
73 each RSV-RTI hospital episode (and other-pathogen-RTI), we calculated the number of bed days
74 as the length of stay (LOS) in days among children under 5 years in each country. We reported
75 the median LOS for RSV-RTI and other-pathogen-RTI, and the distribution of hospital episodes
76 by fine LOS groups (<1 day, 1-day interval between 1 and 7 days, 8-14 days, 15-29 days, and 30+
77 days) for RSV-RTI and other-pathogen-RTI, separately.

78 **Results**

79 **Birth month**

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

90 We found the strongest positive correlation when moving the RSV seasonality series ahead by 2
91 months relative to the birth cohort series, with the Pearson's correlation coefficients ranging
92 from 0.64 (95%CI 0.55-0.72) in Denmark to 0.91 (95%CI 0.83-0.95) in the Netherlands. We
93 found the strongest negative correlation when lagging the RSV seasonality series by 3 months
94 relative to the birth month series in the countries except for Norway (4 months for Norway),
95 and the Pearson's correlation coefficients ranged from -0.45 (95%CI -0.56 to -0.33) in Finland to
96 -0.66 (95%CI -0.82 to -0.40) in the Netherlands(detailed Pearson's correlation coefficients in
97 appendix Figure S1). In line with Figure 1, the correlation coefficients suggested that infants
98 born 2 months before the peak month of RSV admissions were more likely to have the highest

99 RSV-RTI admission rates during the first year of life, and infants born 3-4 months after the peak
100 month tended to have the lowest RSV-RTI admission rates during the first year of life (appendix
101 Figure S1). The median ratio between the highest rates and lowest rates ranged from 3.2 (IQR,
102 2.8-3.6) in Scotland to 10.2 (IQR, 4.4-17.6) in Finland.

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

104 RSV-RTI caused between 4,131 and 34,996 bed days annually in Scotland, England, the
105 Netherlands, Finland, Denmark, and Norway, and 2,817 bed days annually in the Veneto Region
106 of Italy (appendix Table S4). Between 70% (Norway) and 89% (the Netherlands) of these bed
107 days were in infants <1 year. After accounting for country population statistics, RSV-RTI were
108 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
109 years annually, 40.3 (40.1-40.4) to 91.2 (90.6-91.8) bed days per 1,000 infants aged <1 year
110 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
111 Table S4). Compared to other-pathogen-RTI admission, the annual number of bed days for RSV-
112 RTI admission was 1.5-3.5 times higher in children under 5 years across the countries (appendix
113 Table S5). By narrower age bands, the annual average number of bed days for RSV-RTI was 2.8-
114 7.9 times higher than other-pathogen-RTI in infants <3 months, 2.3-9.3 times higher for 3-5
115 months, 1.1-4.8 times higher for 6-11 months, while lower (0.4-0.9 times) for children aged 1-4
116 years (appendix Table S5).

117 **Young infants and underlying medical conditions**

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

121 all the countries, children under 5 years with underlying medical conditions had a
122 disproportionate number of bed days (5-47% of the bed days in children under 5 years versus 3-
123 26% of the RSV-RTI hospital episodes). The longer hospital stay for young infants and children
124 with underlying medical conditions was not RSV-specific, as similar patterns were also observed
125 for other-pathogen-RTI (detailed results in Table S7-S8, Figure S3).

126 **Length of hospital stay for RSV-RTI by country**

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

140 [Discussion](#)

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

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

162 admissions are only found in England [16]. Consistent with our result, the English study found
163 that infants born in September-November during 2010-2014 had the highest odds (odds ratio
164 of 2.1-2.4) of a positive RSV test during their first year of life compared to those born in
165 January. Similar results were also found in two subnational studies in Spain and the
166 Netherlands, as well as in a multi-center Spanish study [10, 11, 23]. In contrast, another Dutch
167 study on patients in general practice found that being born during April-September was
168 associated with higher odds of RSV lower respiratory tract infections compared to other periods
169 [13]. The RSV-RTI general practice episodes peaked during November-December, about 1-2
170 months earlier than the peak of RSV hospital episodes we observed in the Netherlands. This
171 may explain the shift of “high-risk” birth months [24, 25]. A Danish study did not find a
172 significant association between birth timing (in season) and RSV-associated admissions, but this
173 study was not adequately powered [26].

174 The country-specific estimates of bed days show the burden of RSV-RTI in children under 5
175 years on secondary care services. The average annual number of bed days due to RSV-RTI per
176 1,000 population was 10-65 times higher in infants <1 year than in children aged 1-4 years
177 across the 7 countries, highlighting the substantial RSV-RTI burden among infants.

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

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

192 Limitations of this study are similar to those in our previous study [7]. We used ICD codes to
193 identify RSV-RTI admissions (and other-pathogen-RTI). We previously verified that the total
194 counts and age distribution of RSV-coded admissions were comparable to that of RSV-
195 confirmed admissions based on laboratory records in both Scotland and Finland [7].

196 Unfortunately, this verification cannot be extrapolated to other countries. Additionally, we
197 were unable to assess bias in testing or under-detection due to the unavailability of laboratory-
198 confirmed RSV-negative records. The lack of coding of causal pathogens for a large proportion
199 of RTI admissions (between 7% in England and 23% in the Netherlands were pathogen-coded)
200 [7] might suggest that we have underestimated the true number of bed days for RSV-RTI and
201 other-pathogen-RTI. The association between birth month and RSV-RTI admission rates might
202 be affected if differences in coding and viral testing practices exist between the RSV season and
203 the rest of the year. Given the differences in coding and viral testing practices between
204 countries, country-specific estimates might have been affected to varying degrees. Coding
205 practices could have also changed over time. For example, the proportion of RTI hospital

206 admissions with any pathogen-specific codes decreased in England and Scotland since 2013,
207 and this indicates that estimates of bed days for the two nations could have been
208 underestimated to a larger degree in the most recent years [7]. Our future work is to generate
209 estimates of RSV hospital burden using the time-series modelling approach, which can reduce
210 coding related biases. Hospital-acquired infections were not excluded in our analyses; estimates
211 of bed days and LOS could have been biased due to the mis-attribution of hospital stays before
212 acquiring the RSV infection, especially in children with underlying medical conditions. Since RSV
213 burden could be influenced by climate, socioeconomic and other environmental factors [1], the
214 estimates for Veneto Region of Italy may not be representative of the whole country.
215 Additionally, the country population statistics used to estimate rates of bed days could also be
216 biased due to errors in data collection (population registers and censuses) [28]. Conclusions
217 This analysis of multi-year, nationally representative hospital databases in 7 European countries
218 provides high-quality evidence to support country secondary care services planning and future
219 decision making related to national RSV intervention strategies. The estimates provide evidence
220 to support evaluation of RSV intervention programmes. RSV disease prevention therapies
221 (monoclonal antibodies and maternal vaccines) given to infants could help prevent a substantial
222 number of bed days due to RSV-RTI. Our results from the birth month analysis should inform
223 future development of RSV immunisation schedules.

[Footnote page](#)

Study Group Members

The RESCEU investigators are as follows: Rachel M Reeves, You Li, Xin Wang, Harry Campbell, Harish Nair (University of Edinburgh, Scotland); Maarten van Wijhe, Thea Kølsten Fischer, Lone Simonsen (Roskilde University, Denmark), Ramona Trebbien (Statens Serum Institut, Denmark); Caroline Klint Johannesen (Nordsjællands Hospital, Denmark); Sabine Tong (Sanofi); Mathieu Bangert, Clarisse Demont (Sanofi Pasteur); Toni Lehtonen (Finnish Institute for Health and Welfare, Turku University Hospital, Finland); Terho Heikkinen (University of Turku and Turku University Hospital, Finland); Anne C Teirlinck, Michiel van Boven, Wim van der Hoek, Nicoline van der Maas, Adam Meijer (National Institute for Public Health and the Environment (RIVM), the Netherlands); Liliana Vazquez Fernandez, Håkon Bøas, Terese Bekkevold, Elmira Flem (Norwegian Institute of Public Health, Norway); Luca Stona, Irene Speltra, Carlo Giaquinto (Penta, Italy); Eugenio Baraldi, Daniele Donà (Università di Padova, Italy); Arnaud Cheret (Janssen); Amanda Leach, Sonia Stoszek (GlaxoSmithKline); Philippe Beutels (University of Antwerp, Belgium); Louis Bont (University Medical Centre Utrecht, the Netherlands); Andrew Pollard (University of Oxford, UK); Peter Openshaw (Imperial College, UK); Michael Abram (AstraZeneca); Kena Swanson (Pfizer); Brian Rosen (Novavax); Eva Molero (Synapse Research Management Partners).

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.

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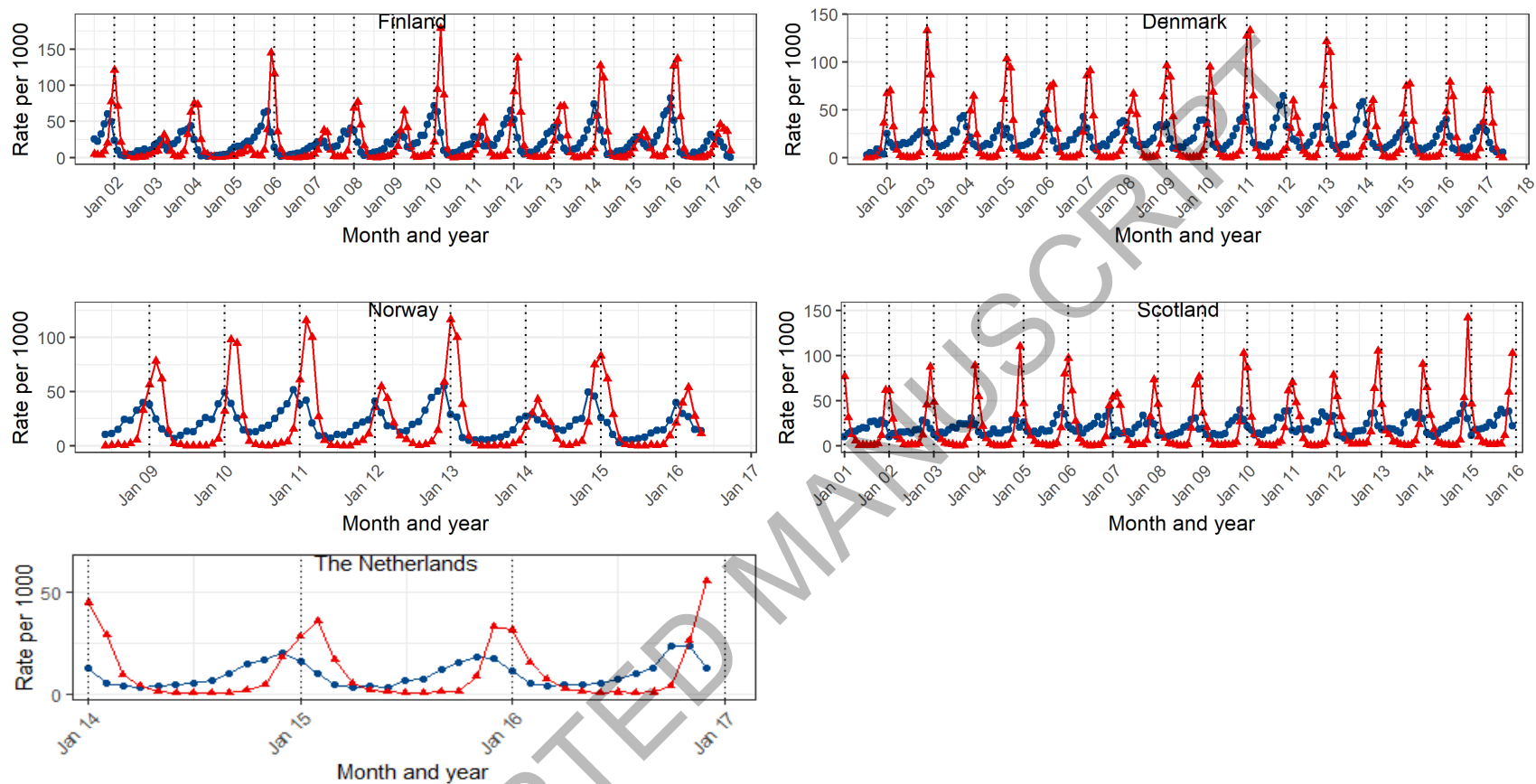


Figure 1. RSV-RTI admission rates per 1,000 infants <1 year by birth month and calendar month in Finland, Denmark, Norway, Scotland and the Netherlands. Blue points are hospital admission rates of RSV-RTI per 1,000 live births by birth month; red points are annualised rates of RSV-RTI per 1,000 infants by calendar month. Dotted vertical lines denote January of each observation year.