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Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016

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Respiratory syncytial virus (RSV) is considered the most common pathogen causing severe lower respiratory tract infections among infants and young children. We describe the seasonality and geographical spread of RSV infection in 15 countries of the European Union and European Economic Area. We performed a retrospective descriptive study of weekly laboratory-confirmed RSV detections between weeks 40/2010 and 20/2016, in patients investigated for influenza-like illness, acute respiratory infection or following the clinician's judgment. Six countries reported 4,230 sentinel RSV laboratory diagnoses from primary care and 14 countries reported 156,188 non-sentinel laboratory diagnoses from primary care or hospitals. The median length of the RSV season based on sentinel and non-sentinel surveillance was 16 (range: 9–24) and 18 (range: 8–24) weeks, respectively. The median peak weeks for sentinel and non-sentinel detections were week 4 (range: 48 to 11) and week 4.5 (range: 49 to 17), respectively. RSV detections peaked later (r = 0.56; p = 0.0360) and seasons lasted longer with increasing latitude (r = 0.57; p = 0.0329). Our data demonstrated regular seasonality with moderate correlation between timing of the epidemic and increasing latitude of the country. This study supports the use of RSV diagnostics within influenza or other surveillance systems to monitor RSV seasonality and geographical spread.

Background

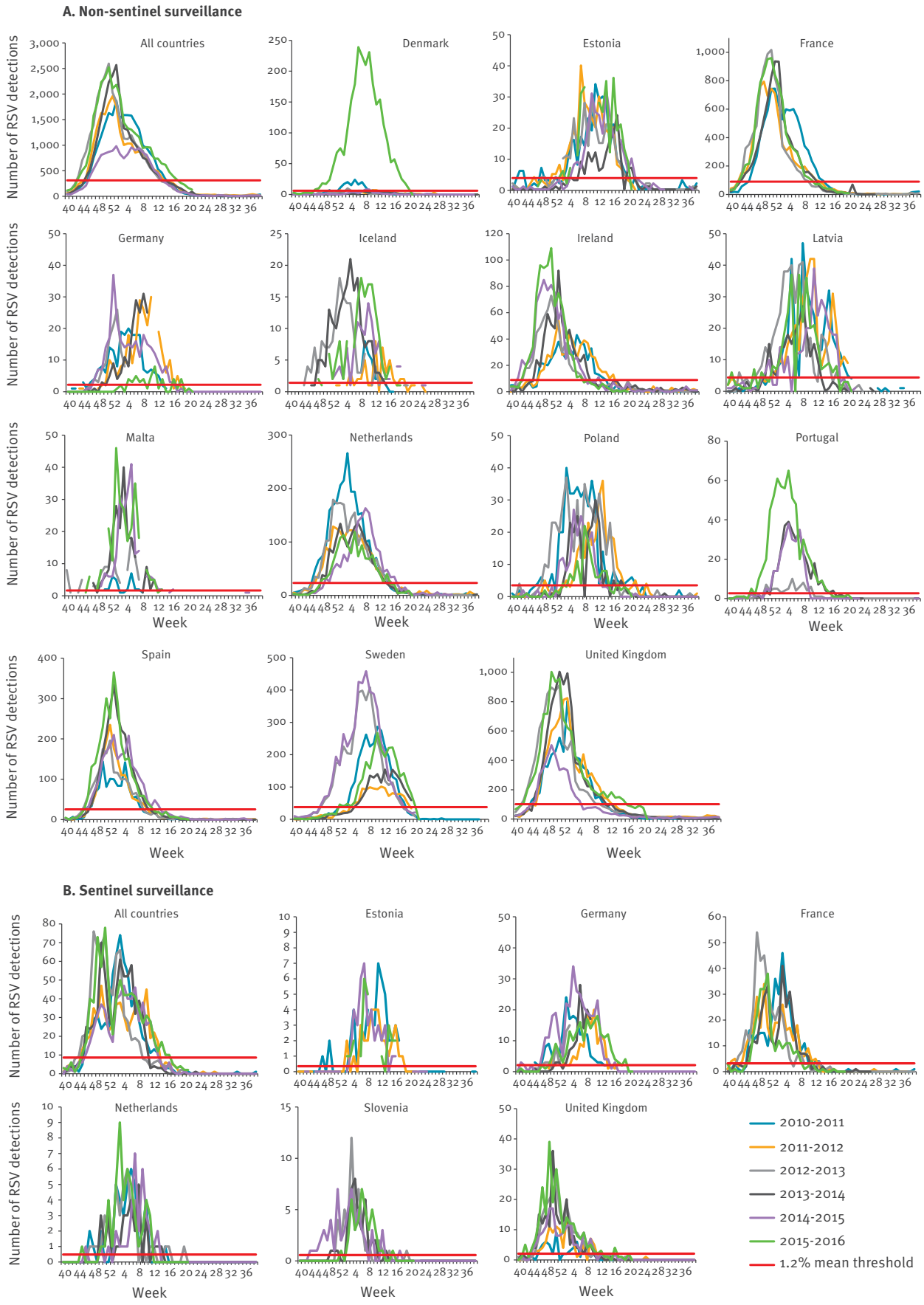
Respiratory syncytial virus (RSV) is considered the major pathogen causing severe lower respiratory tract infections among infants and young children [1]. RSV is the most common cause of hospitalisation for acute lower respiratory tract infection in children younger than 5 years and is estimated to cause between 66,000 and 199,000 deaths worldwide every year [2]. Its significance in causing substantial morbidity and hospitalisation in the first year of life has been affirmed in a recent study and a meta-analysis [3,4]. In England, average annual hospital admission rates are 35.1 per 1,000 children younger than 1 year and 5.31 per 1,000 children aged 1–4 years [5]. In addition to children, RSV causes a substantial disease burden in elderly people and patients with chronic obstructive pulmonary disease [6,7].

RSV causes seasonal epidemics worldwide [8], with one to two epidemics each year [9] following latitudinal gradients in timing, duration, seasonal amplitude and between-year variability [8,9]. In some studies, the seasonal periodicity has been connected to climatic factors [9-11], but a common factor that explains all observed periodicity has not been established. Meteorological conditions such as temperature and high relative humidity have been reported as important predictors of RSV epidemics [9,12]. In the United States (US) and Japan, annual national and regional variation of RSV season onset and end has been reported [13-15]. In the Nordic countries, a major outbreak often alternates with a minor one, with the minor peak in the spring and a major one the following winter [16-19], a phenomenon reported also in Croatia [20], Denmark [21] and Germany [22]. RSV antigenic groups A and B alternate in two-year cycles in Finland, with dominance of the group A viruses in years 1981–82, 1985–86 and 1989–90 and the group B viruses 1983–84 and 1987–88 [17,19], and different genotypes dominate the circulation in consecutive epidemics in Korea [23]. In Spain, no biennial rhythm has been detected but rather a stable annual epidemic with a peak between week 52 and week 1 and circulation 2–8 weeks earlier than influenza viruses [24]. Similarly, in the United Kingdom (UK), one stable epidemic per year is observed [5].

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Figure 1

Non-sentinel (n = 14 countries) and sentinel (n = 6 countries) RSV detections by country, season and week of detection, EU/EEA, 2010–2016



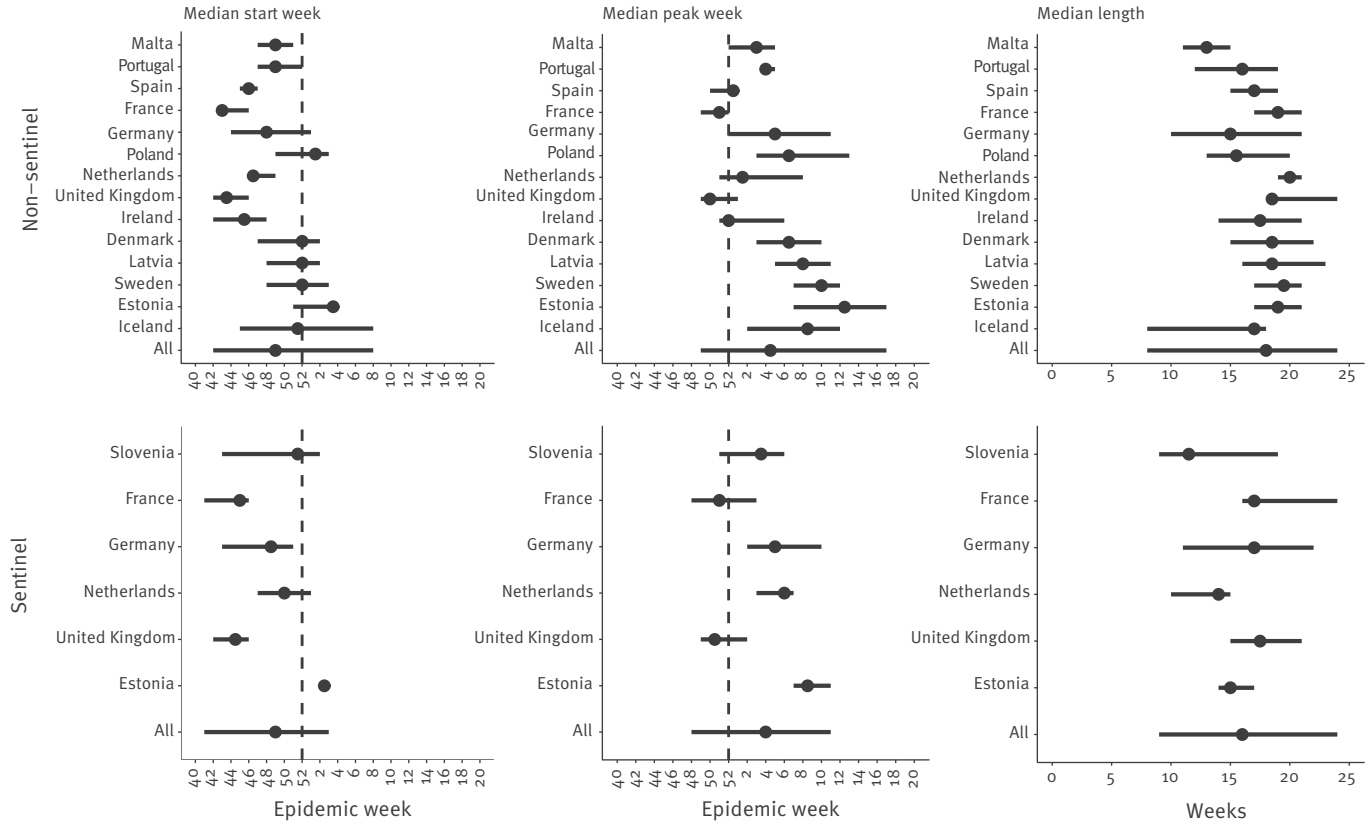
EU/EEA: European Union/European Economic Area; RSV: respiratory syncytial virus.

The top left panel shows the pooled data for all included EU/EEA countries. Other panels show country-specific data by season.

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Figure 2

Timing of RSV season as observed by non-sentinel (n = 14 countries) and sentinel (n = 6 countries) surveillance, EU/EEA, 2010–2016



EU/EEA: European Union/European Economic Area; RSV: respiratory syncytial virus.

Left panels: median start week of RSV season start; middle panels: RSV season peak; Right panels: median RSV season length. Upper panels: observed by non-sentinel surveillance (14 countries); lower panels: observed by sentinel surveillance (6 countries). The dots represent the median value of a given country and the ends of the bars the minimum and maximum values of the range observed. The shift between the years is indicated by a dashed vertical line. Countries are displayed in order of increasing latitude coordinates of their barycentre. 'All' shows median, minimum and maximum values of the pooled results from all countries per surveillance system.

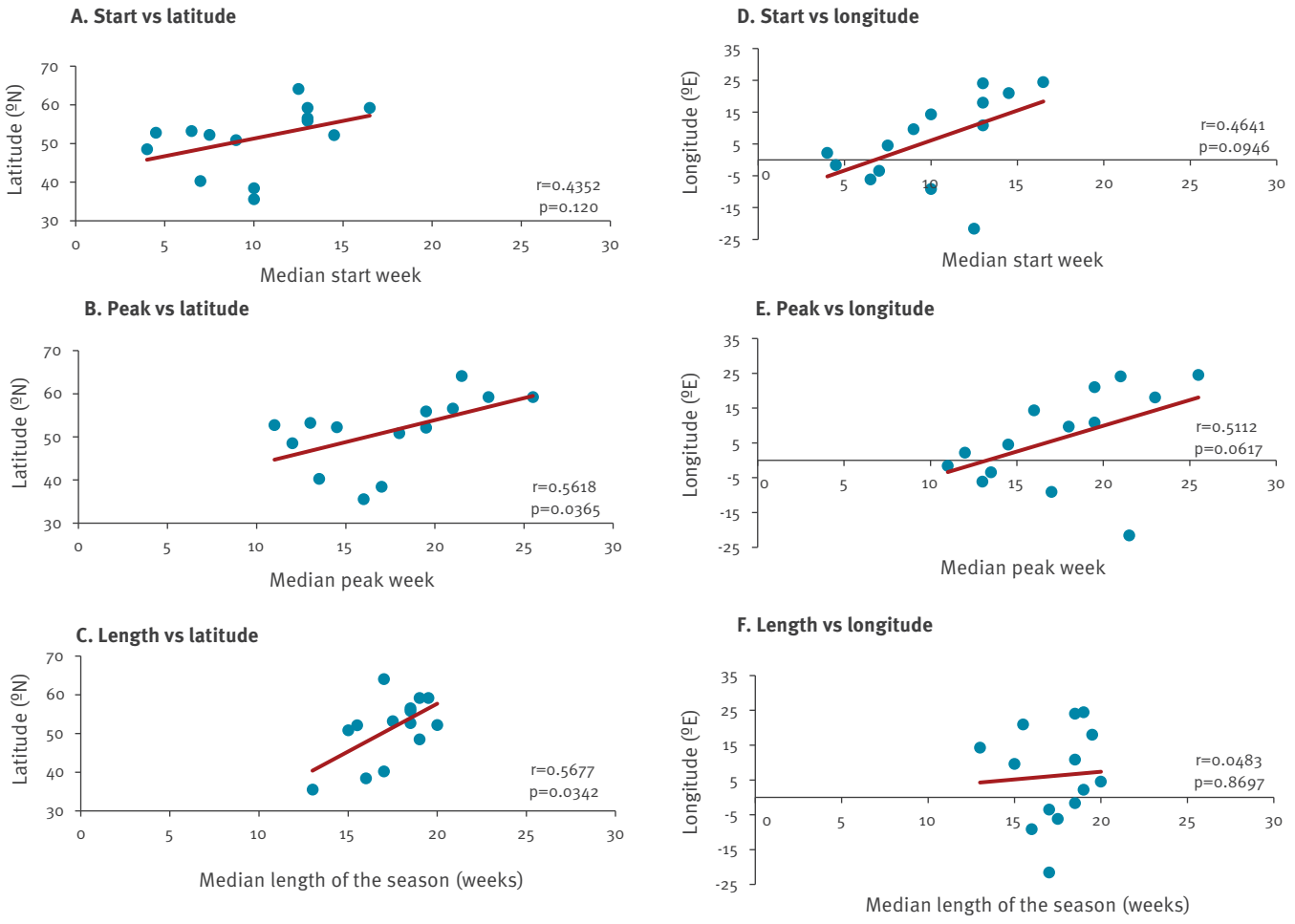
Immunoprophylaxis to prevent RSV infection with a neutralising monoclonal antibody, palivizumab, has been developed for administration to target groups on a monthly basis during the RSV season [25]. However, this drug is limited to high-risk infants, the cost prohibits its use in low- and middle-income countries and the data on effectiveness of the drug in children at high risk other than infants born at gestational age < 33 weeks and in children with chronic lung and heart diseases are limited [26]. The demonstrated high disease burden of RSV infection has created a longstanding interest in RSV vaccines. Approximately 60 RSV vaccine candidates are in preclinical to phase III clinical trials [27,28], with potential target groups including elderly people, pregnant women and infants. A vaccine is expected to enter the market within 5–10 years, presumably by 2025 [29]. As natural infection provides only limited protective immunity owing to evolution of the surface protein G and alternating dominance of antigenic groups A and B [30], most of the vaccine candidates target the fusion protein F, which is cross-reactive across RSV subtypes [27]. To circumvent issues with alternating strains, it has been also suggested to consider inclusion of both RSV A and B in a future RSV vaccine [30]. To plan optimal future vaccination strategies, it is critically important to understand who is affected by RSV and to identify which groups are at risk of more severe RSV infection requiring hospitalisation or intensive care. RSV infection is not notifiable in the European Union (EU) and European Economic Area (EEA), except in Ireland, but many countries have a long tradition of reporting laboratory-confirmed RSV infections at national and international level. The European Influenza Surveillance Network (EISN) collects RSV data for the purpose of interpreting the reports of influenza-like-illness (ILI); these data can also be used to analyse seasonality of RSV [31].

Inter-country comparative analysis of seasonal circulation of RSV across Europe is lacking as most of the published literature focuses on individual countries. Our study describes the seasonality of RSV in 15 countries in the EU/EEA, specifically the start and peak of the season, length of the season and geographical

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Figure 3

Correlation between the RSV seasonal timing and geographical location of the reporting country, non-sentinel data, EU/EEA, 2010–2016 (n = 14 countries)



ºE: degrees east; ºN: degrees north; EU/EEA: European Union/European Economic Area; RSV: respiratory syncytial virus.

The dots represent the individual data points for each country. The linear regression line of the correlation with correlation coefficient (r) and p value are indicated in each graph.

For calculation purposes, the calendar weeks were transformed into running numbers starting with 1. Calendar week 40 thus became week number 1, calendar week 41 week 2 etc. Week 53 was removed from the dataset.

spread, as a baseline description of RSV circulation in Europe. We further aimed to test if the data reported through influenza surveillance systems in use in EU/EEA countries are appropriate to analyse RSV seasonality, including more countries and a more detailed analysis than previous studies.

Methods

Study design

We retrospectively studied laboratory-confirmed RSV detections reported weekly through EISN to the European Surveillance System (TESSy) hosted at the European Centre for Disease Prevention and Control (ECDC) between week 40/2010 and week 20/2016.

Study population and data

We included reports of laboratory-confirmed RSV infection based on PCR, antigen detection, serum antibody detection or virus isolation. Clinicians used either case definitions for ILI or acute respiratory infection (ARI) as the indication for sampling, or their own judgment and diagnostic need rather than a specific case definition [32]. The specimens received from clinicians were tested for RSV in local or national laboratories, and positive results were collected through national surveillance systems. Weekly aggregated data were reported from each participating country through TESSy and covered sentinel surveillance in primary care and/or non-sentinel surveillance in primary- and/or hospital-care facilities where sampling is done for diagnostic purposes. The EU/EEA countries' national

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Table

RSV case definitions used for sampling, geographical location and numbers of RSV detections, by country and surveillance system, 15 EU/EEA countries, 2010–2016

Country name	Case definition for sampling	Surveillance system (sentinel or non-sentinel)	Latitude of the barycentre (°North)	Longitude of the barycentre (°East)	Number of RSV seasons included	Total number of detections	Mean number of detections per season	Minimum number of detections per season	Maximum number of detections per season
Malta	ILI	Non-sentinel	35.9	14.5	5	840	168	34	264
Portugal	ILI	Non-sentinel	39.7	−9.2	4	1,305	326	79	626
Spain	Laboratory-confirmed RSV infection; testing based on clinical judgement	Non-sentinel	39.7	−3.3	6	12,706	2,118	1,278	2,965
Slovenia	ARI, ILI	Sentinel	46.2	14.9	4	191	48	41	59
France	ARI, ILI	Non-sentinel	47.1	2.7	5	45,131	9,026	8,500	9,801
	ARI, ILI	Sentinel	47.1	2.7	5	1,611	322	243	382
Germany	ILI	Non-sentinel	50.9	9.7	6	1,102	184	51	285
	ARI, ILI	Sentinel	50.9	9.7	6	1,046	174	56	336
Poland	ILI	Non-sentinel	51.7	19.3	6	1,748	291	132	464
The Netherlands	Laboratory-confirmed RSV infection; testing based on clinical judgement or ARI[a]	Non-sentinel	52.1	5.3	6	11,715	1,953	1,402	2,760
	ILI	Sentinel	52.1	5.3	5	200	40	32	50
United Kingdom	ARI, ILI	Non-sentinel	52.7	−1.6	6	50,716	8,453	4,747	10,999
	ARI, ILI	Sentinel	52.7	−1.6	6	1,033	172	63	276
Ireland	Laboratory-confirmed RSV infection; testing based on clinical judgement; notifiable since 2012[b]	Non-sentinel	53.1	−7.4	6	4,443	741	547	945
Denmark	2010/11–2014/15: ARI, ILI; 2015/16: testing based on clinical judgement[c]	Non-sentinel	55.9	10.9	6	3,006	501	45	2,568
Latvia	Laboratory-confirmed RSV infection; testing based on clinical judgement	Non-sentinel	56.8	24.4	6	2,187	365	239	442
Sweden	Laboratory-confirmed RSV infection; testing based on clinical judgement	Non-sentinel	58.9	15.4	6	18,736	3,123	1,419	5,118
Estonia	ARI, ILI	Non-sentinel	59.0	25.5	6	1,849	308	177	373
	ILI	Sentinel	59.0	25.5	4	149	37	34	48
Iceland	Laboratory-confirmed RSV infection; testing based on clinical judgement	Non-sentinel	64.4	−21.1	6	704	117	32	193
Total		Non-sentinel			6	156,188	1,977	32	10,999
Sentinel		Sentinel		6	4,230	132	32	382	

ARI: acute respiratory infection; EU/EEA: European Union/European Economic Area; GP: general practitioner; ILI: influenza-like illness; RSV: respiratory syncytial virus.

[a] ARI used in sentinel patients; however, RSV detections reported as non-sentinel detections [38,39].

[b] Irish case definition for notification of RSV since 2012 [40].

[c] In seasons 2010/11 to 2014/15, all diagnostic (ARI/ILI) and sentinel specimens (ILI). In season 2015/16, all RSV-positive laboratory results from the Danish National Microbiology Database including detections from hospitals and GPs.

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operational contact points for influenza surveillance were consulted regarding the use of case definitions and diagnostic detection methods. The reports were dated by date of specimen collection or date of laboratory diagnosis.

Data were included if a country reported for a minimum of four seasons and 5 weeks per season, with at least 24 RSV detections per country, season and surveillance system.

To explore geographical spread of RSV infections across the EU/EEA over time, latitude and longitude of the population centre (barycentre) of each country in decimal degrees were identified. Barycentres were calculated based on the 1 km population density grid provided by Eurostat, using the 2011 population data [33], except for Iceland for which the latest available population data were from 2006.

Data analysis

In line with similar previous work, RSV epidemic seasons were defined as the weeks when RSV detections exceeded 1.2% of total RSV-positive specimens per country, surveillance system and season [8]. RSV detections also had to exceed the threshold continuously during the season (one gap week was allowed). Sentinel and non-sentinel data were analysed separately. Average threshold values over the seasons were calculated separately per country and surveillance system.

Based on the season-specific epidemic thresholds, we calculated the median weeks in which the RSV season started and peaked as well as the median length of the seasons. The start of the season was defined as the first week when the weekly RSV detections exceeded this threshold. The season peak was defined as the week in which the maximum number of RSV detections were reported. If two weeks had the same number of detections, the first week with this number was defined as the peak week.

The correlation between timing of the epidemic and distance of countries' barycentre from the equator (latitude) and Greenwich meridian (longitude) was studied by applying Pearson's correlation to the median start and peak weeks as well as the length of each RSV epidemic; this was based on data from 14 of the 15 participating countries providing non-sentinel data. Western longitudes were transformed to Eastern longitudes. Residues were tested for normal distribution by Shapiro–Wilk test. Any correlation (r) of 0–0.19 was regarded as very weak, 0.20–0.39 as weak, 0.40–0.59 as moderate, 0.60–0.79 as strong and 0.80–1 as very strong [34]. The threshold of significance was set at $p = 0.05$. Fitted values of the correlation, the equation of the trend line and R^2 values (goodness of fit of the regression line) were calculated. Data were analysed with Microsoft Excel 2013 and Stata 14.

Results

Countries reporting RSV detections

Fifteen EU/EEA Member States reported 160,418 RSV detections during the study period: 156,188 through non-sentinel systems (14 reporting countries) and 4,230 through sentinel surveillance systems (six reporting countries) (Table). At the non-sentinel sites, four countries used the ILI case definition only, four used the ILI and ARI case definitions and six used sampling for RSV based on clinical judgement without specific case definition (Table). At the sentinel sites, two countries used the ILI case definition only and four used both ILI and ARI case definitions. Eleven countries reported non-sentinel data for all six seasons (Table). The mean number of non-sentinel detections per season ranged from 117 in Iceland to 9,026 in France. The mean number of sentinel detections per season ranged from 37 in Estonia to 322 in France.

In Denmark, the surveillance system changed in 2015/16 from an ILI/ARI-based system to register-based retrieval of RSV-positive laboratory results from the Danish National Microbiology Database including detections from hospitals and general practitioners. Two countries, France and the UK, contributed 61% of the non-sentinel and 63% of the sentinel detections and therefore, their data influenced the overall European estimates the most.

Seasonality

Seasonality was observed by both types of surveillance (sentinel and non-sentinel) with the season threshold crossed in all countries in all years for both (Figure 1). All RSV seasons from 2010/11 to 2015/16 had a similar timing and epidemic course across Europe with some variation within and between countries (Figure 1). The highest numbers of detections were reported in seasons 2012/13, 2013/14 and 2015/16. In peak weeks, more than 2,500 specimens per week were reported positive for RSV. The lowest figures were observed in 2014/15 when France did not report RSV detections to TESSy because of a switch from one surveillance system to another during that season. Each year, the RSV epidemic in Europe progressed rapidly after week 40 to its peak and decreased to baseline levels only around week 20, which was probably driven by the later timing of the RSV epidemics in the countries with more northerly location (see below). Although the sentinel dataset was considerably smaller than the non-sentinel one, the sentinel detections followed similar patterns as non-sentinel detections and both showed a considerable effect of the end of year holiday period (weeks 52–1) (Figure 1 B) which is not as visible in the non-sentinel data (Figure 1 A). For the sentinel data, the decrease in detections during the end-of-year holiday period was mainly shown in data from Germany (Figure 1 B). While only eight detections of RSV in weeks 21–39 were reported from sentinel sources over the study period, RSV was detected by non-sentinel surveillance throughout the year, albeit at low levels (18 detections

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per week on average) during weeks 21–39. Compared with the remaining seasons, the season started 2–7 weeks earlier in Denmark, Germany, Iceland, Ireland, Latvia, Malta, Poland and Sweden in 2012/13 and in Germany, Poland and Sweden in 2014/15 (Figure 1 A).

Based on analysis of the individual countries separately or as a group, the median start of the RSV season was in week 49 in both surveillance systems (ranging from week 41 to week 3 for the sentinel and from week 42 to week 8 for the non-sentinel data; Figure 2). The median peak week was in week 4 (range: 48 to 11) and 4.5 (range: 49 to 17), respectively, for sentinel and non-sentinel detections, roughly six weeks after the epidemic started. The median length of the RSV seasons based on sentinel and non-sentinel surveillance was 16 (range: 9 to 24) and 18 weeks (range: 8 to 24), respectively (Figure 2).

Geographical spread

RSV detections peaked later with increasing latitude (Figure 3). There was a moderate positive correlation of latitude with the peak week ($r=0.56$; $p=0.0360$) and the length of the season ($r=0.57$; $p=0.0329$). This corresponds to earlier peak and shorter seasons in the southern parts of the EU/EEA. For start and peak of the season, there were moderate correlations ($r=0.52$ and $r=0.47$, respectively) to increasing longitude, although without statistical significance ($p=0.0563$ and $p = 0.0899$, respectively).

Discussion

In this study, we showed that in the 15 European countries reporting RSV surveillance data to the ECDC TESSy database, the average RSV season started in the beginning of December, peaked in early February and continued until early April, however, with wide variation between the countries. The data also showed a correlation between the earliest peak and a southerly latitude as well as between a longer season and a more northerly latitude. Furthermore, we showed that RSV seasonality can be captured through weekly reporting of RSV detections driven by diagnostic testing, using influenza ARI and ILI sentinel and non-sentinel surveillance systems. With these results, our analysis contributes to the understanding of the seasonality of RSV epidemics in Europe.

As previously shown in a global literature review and study [8], we confirmed in this study a latitudinal gradient of RSV epidemics peaking later and lasting longer with more northerly location of a country in the EU/EEA. We also showed a moderate correlation of the start and peak of the season with increasing longitude, although not statistically significant. The global study observed a weaker latitudinal gradient than our study, possibly because one third of the study sites were in the tropics [8]. In our study, all reporting countries were from the temperate climate zone in the northern hemisphere. In the global study, the northern hemisphere temperate zone covered study sites from the US to Asia, and the range for median RSV peak time was from December to February, with an epidemic duration of up to six months. The peak of the RSV epidemic in our study as well as its duration of slightly over four months is well in line with the range presented in the review [8] and in a study including seven countries from tropical and subtropical areas where the median length of a season was five months [9].

The median start week for RSV in Europe (week 49) was almost the same as for the US season which starts in week 51 (late December; range: weeks 46 to 3) [13]. The European and US epidemics both peak very close to each other: week 4 to 4.5 in our EU/EEA data and week 5 in the US [13]. Regions of the US experience significant geographical variability in the start of the RSV season corresponding to changes in longitude and latitude: in the southern states, the season starts in late November, in the Midwest in early January [13] and in Alaska between mid-October and late December [35]. In the US, an overall south-to-north gradient is usually observed for the start of the RSV epidemic [13].

The length of 13–17 weeks of the RSV season in the US [13] is a little shorter than what we observed (16–18 weeks). Interestingly, the RSV epidemics last longer in the south of the US than in the rest of the country. We observed the opposite, a statistically significant positive linear correlation between latitude and season length in the 14 studied EU/EEA countries, i.e. the further north the barycentre, the longer the RSV season. Further work is required to understand climatic and other factors which may be responsible for this correlation with latitude.

Two-year periodicity of RSV circulation has been observed in national studies in Croatia [20], Finland [17,19], Germany [22], Norway [16] and Sweden [18]. We observed an earlier start to the season only for the 2012/13 season in eight of the 15 countries and for 2014/15 in three countries. Some sporadic changes in the season start weeks and lengths were also observed.

Before the introduction of an RSV vaccine, RSV surveillance is required to document the baseline burden of disease, and the World Health Organization (WHO) is developing RSV surveillance [36] and following the RSV vaccine development with interest [29]. As no international RSV case definition has yet been agreed, the WHO has proposed candidate case definitions for severe and very severe RSV-associated lower respiratory tract infections as endpoints for RSV vaccine trials [29]. Further work is required to determine the optimal case definitions that can be applied to RSV surveillance, especially surveillance of severe outcomes. We observed that the sentinel systems detected considerably fewer RSV cases than the non-sentinel system detections, which is a reflection of the sentinel system being designed to capture only a proportion of the population under surveillance and screening mostly

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for influenza. The overall low numbers in sentinel systems also reflect the lower number of participating countries, and therefore lower overall population size, reporting through such a surveillance system.

Our study has a number of limitations that need to be considered when interpreting the results. Only 15 of the 30 EU/EEA Member States reported RSV detections and a large proportion originated from only two countries (France and UK), causing a skewed distribution. Therefore, results of this study should not be seen as representative for the entire EU/EEA, in particular for countries with smaller populations. No data on the patients' ages were available and therefore analysis by age group was not possible. TESSy did not have an RSV-specific denominator of specimens tested in this data collection period, nor a population denominator for RSV, and therefore proportions of positive specimens to define season start could not be calculated and weighting factors by population size could not be used. The weighting by population size could have benefited the study by removing the strong emphasis on the data from France and the United Kingdom. Using the published method for defining the epidemic threshold [8], the epidemic threshold depends on the total number of detections per country and season and may thus be very low in a small country or during a low-intensity RSV season. We acknowledge also that only Ireland applied an RSV-specific case definition, and because the majority of detections were from non-sentinel surveillance, most of the detections were collected based on a diagnostic need. As a large proportion of the data were collected as part of the national influenza surveillance systems, efforts should be made in the future to collect specimens specifically for RSV during the influenza season as focusing mainly on influenza may have caused a bias by detecting less RSV earlier during the autumn or later in spring. The surveillance systems and detection methods were not standardised for RSV detections, many systems changed during the study period and absolute numbers of detections may therefore not be comparable across countries or within countries over time. However, thresholds were calculated by season to detect start and peak of the RSV seasons even if a small number of detections were reported. As the EU ILI case definition that is not well-suited for RSV [37] was applied in some countries, the absolute number of RSV detections may have been underestimated in these surveillance systems. Furthermore, virological data were not available and it would be of interest to study the seasonal patterns of RSV at the level of virus type and genetic clade.

Despite these limitations, the present study showed that virological surveillance systems carried out by influenza reference centres or specialist and routine diagnostic laboratories that report laboratory-confirmed RSV infections can be used to monitor RSV seasonality, confirming findings of the European Influenza Surveillance Scheme [31]. As the start of RSV monthly prophylaxis with palivizumab needs to be timed because the duration of protection is limited, according to the local circulation of the virus, knowing the seasonality at country level is of benefit for public health. At the European level, with RSV vaccines expected to come to the market in the next five to 10 years, it is crucial to establish a baseline for the number of RSV detections or for the weekly proportion of RSV-positive respiratory specimens to understand the extent of RSV circulation before implementing vaccination programmes. Further work is required to determine the design of optimal surveillance systems for RSV to measure the impact of future RSV vaccine programmes on different age groups and on the burden of severe disease. Additional benefits of establishing RSV surveillance standards at the European level include the ability to compare seasonality and trends between countries as well as virus typing and genetic characterisation, and to obtain standardised data on age groups at risk, such as newborns.

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Conflict of interest

None declared.

Authors' contributions

EB initiated the study, wrote the study proposal, managed the data collection, cleaned and analysed the data and wrote the first draft as well as revised the manuscript based on comments from country colleagues and reviewers. MW supported the analysis plan and contributed to the writing of the manuscript. KJ, RS and PP supported the analysis plan as well as critically reviewed the report. RS contributed also to the data maintenance. The network members listed separately supplied and validated the data, described the surveillance systems, and reviewed the report. All authors contributed to the revision of the article. All authors have read and approved the final manuscript.

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