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TITLE: RESPIRATORY SYNCYTIAL VIRUS SEASONALITY: A GLOBAL OVERVIEW.

Pablo Obando-Pacheco[1,2], Antonio José Justicia-Grande[1,2], Irene Rivero-Calle[1,2], Carmen Rodríguez-Tenreiro[1,2], Peter Sly[3], Octavio Ramilo[4,5], Asunción Mejías[4,5], Eugenio Baraldi[4,6], Nikolaos G. Papadopoulos[4,7,8], Harish Nair[4,9], Marta C. Nunes[4,10], Leyla Kragten-Tabatabaie[4,11] Terho Heikkinen[4,12], Anne Greenough[4,13], Renato T. Stein[4,14], Paolo Manzoni[4,15], Louis Bont[4,16], Federico Martinón-Torres[1,2,4].

1 Translational Pediatrics and Infectious Diseases, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Galicia, Spain.

2 GENVIP Research Group, Instituto de Investigación Sanitaria de Santiago, Santiago de Compostela, Galicia, Spain.

3 Children's Lung Environment and Asthma Research, Child Health Research Centre, The University of Queensland, Brisbane, QLD, Australia.

4 Respiratory Syncytial Virus Network (ReSViNET; www.resvinet.org), Utrecht, The Netherlands.

5 Department of Pediatrics, Division of Infectious Diseases, Ohio State University, Columbus, OH, USA; Center for Vaccines and Immunity at Nationwide Children's Hospital, Ohio State University, Columbus, OH, USA.

6 Women's and Children's Health Department, University of Padua, Via Giustiniani 3, 35128, Padova, Italy.

7 Department of Allergy, 2nd Pediatric Clinic, University of Athens, Athens, Greece.

8 Division of Infection, Immunity & Respiratory Medicine, University of Manchester, UK.

9 Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, Scotland, UK.

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10 Respiratory and Meningeal Pathogens Research Unit, and Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of Witwatersrand, Johannesburg, South Africa.

11 Julius Clinical, University Medical Center Utrecht, Zeist, The Netherlands.

12 Department of Pediatrics, University of Turku and Turku University Hospital, Turku, Finland.

13 Division of Asthma, Allergy and Lung Biology, King's College, London, UK.

14 Pediatric Pulmonology Unit, Pontifícia Universidade Católica RS, Porto Alegre, Brazil.

15 Neonataology and Neonatal Intensive Care Unit, S Anna Hospital, Torino, Italy.

16 Department of Paediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands

Corresponding Author: Federico Martinón Torres (FMT). Email: federico.martinon.torres@sergas.es. Tel.: +34 981 955373. Fax: +34 981 950596

Alternative corresponding Author: Pablo Obando Pacheco. Email: pabobapac@gmail.com. Tel. : +34 638 041495

Summary

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infections (ALRI) in children. This is the first study using original source high-quality surveillance data to establish a global, robust and homogeneous report on global country-specific RSV seasonality.

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ABSTRACT

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infections (ALRI) in children. By the age of 1 year, 60–70% of children have been infected by RSV. In addition, early-life RSV infection is associated with the development of recurrent wheezing and asthma in infancy and childhood. The need for precise epidemiologic data regarding RSV as a worldwide pathogen has been growing steadily as novel RSV therapeutics are reaching the final stages of development. To optimize the prevention, diagnosis and treatment of RSV infection in a timely manner, knowledge about the differences in the timing of the RSV epidemics worldwide is needed. Previous analyses, based on literature reviews of individual reports obtained from medical databases, have fail to provide global country seasonality patterns. Until recently, only certain countries have been recording RSV incidence through their own surveillance systems. This analysis was based on national RSV surveillance reports and medical databases from 27 countries worldwide. This is the first study using original source high-quality surveillance data to establish a global, robust and homogeneous report on global country-specific RSV seasonality.

Keywords: RSV; RSV Seasonality; RSV Epidemiology; RSV Epidemics; Acute Lower Respiratory Infections; Respiratory Infections; RSV Surveillance; Surveillance.

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BACKGROUND

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory infections (ALRI) in children. By the age of 1 year, 60–70% of children have been infected by RSV (2–3% of whom are hospitalized), and almost all children have been infected by 2 years of age [1]. This virus is estimated to cause approximately 33.8 million new episodes of ALRI annually in children <5 years of age worldwide, resulting in 3.2 million hospital admissions and 59,600 in-hospital deaths in children <5 years in 2015 [2]. In addition early-life RSV infection is associated with the development of recurrent wheezing and asthma in infancy and childhood [3]

The need for precise epidemiologic data regarding RSV as a worldwide pathogen has been growing steadily as novel vaccines and molecules for the prevention and treatment of RSV infections are reaching the final stages of development [4]. In order to establish timely counter-measures to control the pathogen, information about the different epidemic waves of the virus is needed [4]. Many western countries have included detection of RSV as part of their influenza surveillance system, especially since it was noted that its circulation generally predates that of the influenza virus by six to eight weeks. Nevertheless, many countries have not implemented a routine surveillance system for RSV, or they have done so only in certain regions, or even restricted to specific medical facilities. The aim of this report is to provide an overview of RSV seasonality throughout 27 countries across the world.

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METHODS

We surveyed 27 countries distributed among nine predefined geographical areas for epidemiological data (Figure 1).

Figure 1

Selection strategy

Selection of the regions studied was done through a two-searches approximation conducted between June 2016 to September 2017. A first general search was conducted in Google to detect countries with official surveillance programs producing accessible reports containing information on RSV seasonality. Terms included were "RSV" or "Respiratory syncytial virus" or "Influenza" plus "Surveillance". A total of 19 countries were selected. Most surveillance systems had RSV-specific data available from laboratory detections, but for France we used syndromic "bronchiolitis" data. To complement and compare the information obtained from the official reports and to increase the information gathered in poorly covered areas, a literature review was performed in PubMed of articles published between 1990 and 2017. Keywords included 'respiratory virus', OR 'respiratory syncytial virus,' OR 'RSV,' in combination with 'seasonality' OR 'surveillance'. Only studies reflecting specific information on RSV seasonality (i.e. start, end, peak or duration of the RSV season) were extracted. A total of 8 new countries were added to the initial survey to increase the total number of

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countries studied to the final figure of 27. Only records written in English, Spanish, German, French and Portuguese were included in this study.

Information retrieved

Variables recovered from the different reports were as follow: Start and end of the RSV season (in epidemiological week or month if the specific week was not available), peak of RSV activity (in epidemiological week or month if the specific week was not available), duration of the seasons, presence of official RSV surveillance program, period studied, region variability and usage of laboratory detection. Data for each country were collected by two independent investigators from the ReSVinet (Respiratory Syncytial Virus Network) / GENVIP (Genetics, Vaccines, Infectious Diseases and Pediatrics) research groups.

We relied on data provided by official national reports to establish the start and end of the RSV season, whenever available. In Europe, the first reports with official data about RSV detection are available as early as 1995 for Finland, 1996 for Germany and 1998 for Belgium, and as late as the end of the 2000s for as Spain and UK. In South and Central America, the earliest reports are found in 2009 for Brazil and Argentina. North America RSV official seasonality reports date as early as 1983. With the exception of New Zealand, that presents information regarding RSV since 1997, the rest of the countries studied have accessible data on RSV surveillance starting from the late 2000s. We recovered information from official surveillance organization reports from 2010 onwards whenever possible.

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In countries with no official sources on RSV epidemiology and disease burden, information was systematically extracted from the best reliable medical source at our disposal. Initially, WHO and CDC reports for each of the countries were reviewed, then local and multicenter publications assessing several consecutive RSV seasons were also reviewed, and finally a review of published articles documenting RSV burden limited to a local area or a group of hospitals were used, if no better sources were available. For those countries with no precise information regarding exact timing and duration of RSV season, the onset of RSV season was defined as the first two consecutive weeks when 10% or higher of the total tested samples for respiratory pathogens were positive for RSV. The end of the RSV season was defined similarly when the proportion of positive RSV tests fell below 10% for two consecutive weeks.

RESULTS

Although there were major differences among the 27 countries studied, seasonal RSV epidemics within each individual country were consistent over time. We found that even when global trends were documented and usually repeated over seasons, some variations between different years were observed. Even when most countries included (19 out of 27) had official surveillance systems, information devoted to RSV was usually scarce and embedded within influenza surveillance reports (Figure 2). Almost every sentinel program detected RSV through laboratory methods (excluding France), but almost no information regarding the specifics of the microbiological test used was available in the majority of the reports.

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Table 1 and Figure 2 summarize the RSV seasonality data per country, and a detailed version of Europe is presented in Figure 3.

Table 1

Figure 2

Figure 3

Globally, RSV epidemics started in the South moving to the North. We found that the RSV wave started in most countries situated in the Southern Hemisphere between March and June, and in the Northern Hemisphere between September and December [5–7]. Decrease in RSV activity was observed from August to October in the Southern Hemisphere and from February to May in the Northern Hemisphere [5-7]. Regarding duration, most countries in both hemispheres had seasons that occupied from 5 to 6 months in total. While this was the general rule, shorter seasons were seen in Spain (from 3 to 5 months) [8], UK (from 3 to 4 months) [9] and Israel (4 months) [10] in the northern hemisphere whilst in the southern hemisphere RSV activity in Australia [11] mainly lasts approximately 4 months long. An exception to this patterns was seen in countries were humid or rainy seasons was seen, particularly those near the equatorial area like Mozambique [12,13] or Malaysia [14], were RSV tended to linger longer, up to 10 months duration.

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The seasonality was fairly consistent within most regions, although we observed variations from year to year. These variations were independent of the hemisphere and the majority remained between 1 to 3 weeks difference from season to season in the start, end and/or peak of RSV activity. Most countries showed major variations of 1 month least once during the studied periods. Curiously, these major variations were less appreciated in the regions were no surveillance system was stablished (probably related to the scarce sources of information found). Despite the straight forward trends described, there were some countries that presented irregular patterns. In Germany [15], two differential patterns of RSV seasonality have been detected: an early season starting in October-November and finishing in March-April and a late season starting in December and finishing in May, having both seasons a similar duration. RSV infections in Finland, according to the data gathered from the literature review, follow a two-year cycle [16,17]. A small epidemic in spring of every odd-numbered year, is followed by a major epidemic that starts in November-December and extends to the next spring. Seasonality also follows a distinctive pattern in Mexico [18]. A two-season year is followed by a milder year were the outbreak starts in spring, maintaining activity almost all year round with no clear peaks. Intra-country differences in seasonality were noted, especially in countries with large territories and different regional climatic regions, such as Brazil [19], the USA [20] or Australia [21-23]. Additional details and references on seasonality of RSV by region is available in the supplemental material.

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DISCUSSION

To our knowledge, this is the first study using original source high-quality data relying predominantly on the official information gathered by the different surveillance networks to establish a global report on country-specific RSV seasonality that allowed us to observe the typical worldwide distribution of RSV seasonality at a glance. We have included a wide selection of information retrieved not only from research studies, but also and more importantly, from the actual surveillance systems in the different countries. This method allowed us to obtain better distribution and homogeneity of the information acquired than did studies based exclusively on literature reviews. Those earlier studies usually recorded information in hospital settings, reporting data from few regions or centres, thus failing to establish global country seasonality patterns. Furthermore, we could not find in the literature any other review that reflects the specific ranges in which seasons and RSV peaks of activity vary during the periods studied. Many other original papers are based on regional or single country data, and they have been useful for analysing the circulation of RSV in their respective regions [6,12-14,16-17,19,22-24,27-48].

The first global RSV seasonality study found in the literature was conducted in 2002 by Stensballe et al. [5]. The authors reported different patterns for the Northern and Southern hemispheres and the equatorial region in a city-based format, relying on information provided by medical databases. Haynes et al. [6] worked in conjunction with the Centers for Disease Control and Prevention (CDC) Global Disease Detection Centers to investigate different trends in low- and middle-income countries. They analysed the data in conjunction with the climate patterns. The largest study in the literature was carried out by Bloom-Feshbach et al. [7] where information from 137

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global locations based on a literature review, electronic sources and the WHO surveillance system FluNet was reported. Their study showed seasonal patterns of RSV similar to the present study, with temperate locations of the Northern and Southern Hemispheres characterized by focused peaks of activity during their respective winters, and a wide range of variability in the timing and duration of epidemics in the tropics.

In regard to weather conditions, the general rule in temperate climate regions such as those of Europe or North America, is that RSV activity follows the decrease in temperature. Exceptions were observed in equatorial countries and tropical areas with high humidity, such as the Philippines or Mozambique, where viral circulation is seen primarily during the rainy season, although showing residual activity throughout the year [5–7].

This study is meant to serve as a general guide for RSV seasonality, not only to provide general knowledge about the epidemiology of the virus but also to serve as a basis for actual preventive and therapeutic strategies against RSV using established prophylaxis measures and/or those about to be released to the market. Even though we have highlighted the consistency between seasons and we expect this information to be very useful, it should be considered as a complement for the actual information gathered in real time by the current surveillance systems. Major variations of a month or more that could make a preventive measure useless do occur occasionaly. Therefore, we propose that the best approach to predict RSV outbreaks is to construct a robust, homogeneous, active and global surveillance program with real-time data to help predict the epidemiologic waves in a timely fashion. A number of countries have been recording RSV cases through their own surveillance systems for some years now.

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These countries, however, are part of a minority, and most of them only include RSV surveillance as a secondary detection along with other surveillance campaigns (i.e. influenza virus and bronchiolitis surveillance), with scarce information regarding RSV. In areas without official surveillance systems, one has to rely on single or multicenter studies done by various research groups.

To this respect, the WHO through the Global Influenza Surveillance and Response System (GISRS) is in process of implementing a pilot of RSV surveillance based on the influenza surveillance platform, with 14 countries selected covering for each of the WHO regions [49].

Our approach also allowed us to study the seasonality of RSV for longer periods of time, as RSV surveillance systems have been in operation in some of the areas for many years.

Prevention of the RSV infection could not only protect children from the acute effects of the disease but also improve long-term respiratory morbidity such as recurrent wheezing and asthma [50].

A limitation of our approach is that information collected from middle- and low-income countries is scarce as most of these regions lack RSV surveillance networks. In particular, we acknowledge that certain regions such as Africa are underrepresented in our analysis. As the main approach of this review is describing the seasonality of RSV, we did not analyze further epidemiological data like transmission patterns or activity of other viral pathogens. Although the effect of climate in the different RSV seasonality patterns was observed in the study for different countries, we did not conduct a deep analysis of this fact, as actual meteorological data was not extracted during the review.

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It will be interesting to further develop this idea in following analyses. Although most of the surveillance programs do perform sample testing in subjects with symptoms of respiratory infection, those surveillance networks were influenza like illness is the driver of sampling performance could underestimate RSV epidemic unless Influenza and RSV overlap. Finally, circulation of the different RSV subtypes was not further analyzed, as almost no surveillance network differentiates between the different genotypes. We decided not to include information in this respect as the literature is based on small sample studies carried out for short periods, preventing a global review of the subject.

In summary, this report provides information that may allow prediction of the beginning of outbreaks of RSV across the world. Even when local epidemic waves are consistent between different years, minor changes between seasons are present from year to year. This variability could turn a prophylactic measure into a useless endeavor if, for example, vaccination campaigns against RSV begin when the outbreak has already started. Therefore, as the data has shown, future seasonal RSV vaccinations campaigns should be organized after the different patterns repeated in each region where the program is planned to be implemented. Although a general dissemination pattern exists for RSV, the described variations from season to season justify introduction of new well-organized supranational and country- or region-based RSV-specific surveillance tools to predict these variations, as it has been done for Influenza virus infections in the past. The experience with the Influenza virus model has taught us that the effectiveness of efforts directed towards preventive and prophylactic

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measures would be increased if the seasonal and epidemiological characteristics of the virus waves could be better predicted. As novel RSV therapeutics are expected to soon become available [20], local seasonality data will allow optimizing the prevention, diagnosis and treatment of RSV infections.

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Table 1.

Country	**Start (season week)**	**Peak (season week)**	**End (season week)**	**Season length (weeks)**	**Period studied**	**Region variability**
			<u>EUROPE</u>			
Belgium	39-43	49-50	7-13	18-22	2004-2014	No
France (official, syndromic-based)	35-37	48-52	10-14	25-31	2011-2017	No
France (Unofficial RSV surveillance)	October-November	December	February-March	20-24	2011-2014	No data
Finland	50-1	7-10	17-20	19-21	2010-2015	Yes
Germany	Early 40-47	52	11-15	19-21	2010-2017	No
	Late 50-52	52-16	18	16-22		
Greece	December	February	Apr/May	20	1999-2013	No data
Italy	October	Jan/Feb	April/May	24-30	2000-2014	Yes
The Netherlands	45-49	51-8	15-17	19-23	2010-2016	No data

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Spain	44-45	50-52	6-12	12-19	2010-2017	No
United Kingdom	43-45	49-52	4-6	11-15	2010-2016	No
AMERICA						
North America						
Canada	46-49	52-8	15-18	20-22	2012-2017	Yes
USA	44-46	52-4	12-14	21-23	2011-2017	Yes
Central America						
Guatemala	16-23	30-34	43-47	25-31	2015-2017	No
Mexico	1 35-39	17-18 37-45	17-20 46-47	17-20 7-12	2012-2015	No data
	13-16	20-30	29-42	16-36		
South America						
Argentina	16-19	24-27	35-40	20-22	2011-2017	No
Brazil	7-11	14-19	29-31	19-24	2009-2017	Yes
Chile	19-22	26-32	36-41	16-20	2011-2017	Yes
SOUTHERN AFRICA						

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Mozambique	October	March	May	16-40	1998-2000	No data
South Africa	2-9	10-18	19-33	19-33	2009-2016	No
OCEANIA						
Australia	19-23	27-31	34-38	14-16	2009-2016	Yes
New Zealand	18-20	29-34	35-39	19-23	2010-2015	No
ASIA						
Middle East						
Israel	44-49	51-3	5-9	13-18	2005-2017	No
Southern Asia						
Malaysia	July	Sep-Dec	March	36	1982-2008	No
Philippines	October	Nov-Dec	February	20	2010-2013	Yes
Thailand	April-May	September	November	24	2005-2011	No
East Asia						
China	November	Dec-Feb	April	24	2010-2015	Yes
Japan	30-45	41-50	45-9	14-27	2010-2017	No Data
South Korea	Aug-Oct	Mid Oct-Nov	December	14-20	2008-2016	No Data

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Footnote: Summary of seasonality data organized by region and country. Numbers show the range of epidemiological weeks or months (depending on available data).

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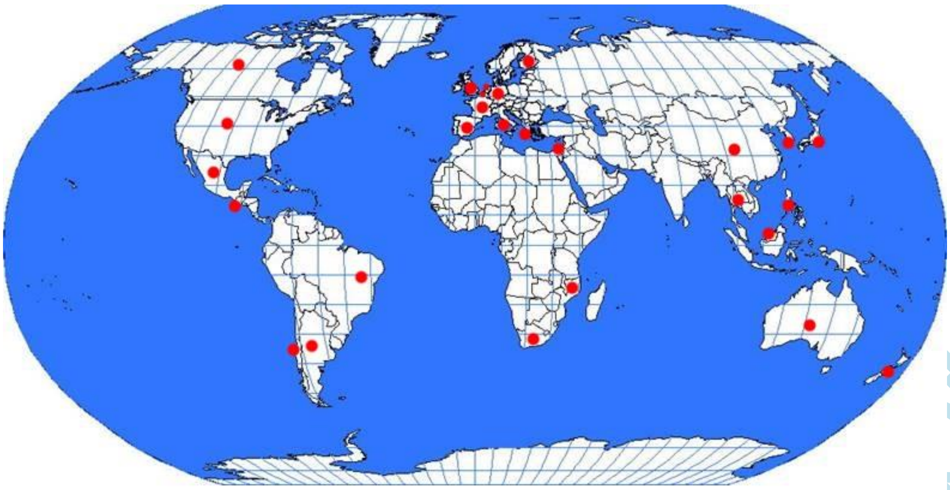

Figure 1. Countries covered by the review.

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USUAL RSV SEASONALITIES WORLDWIDE

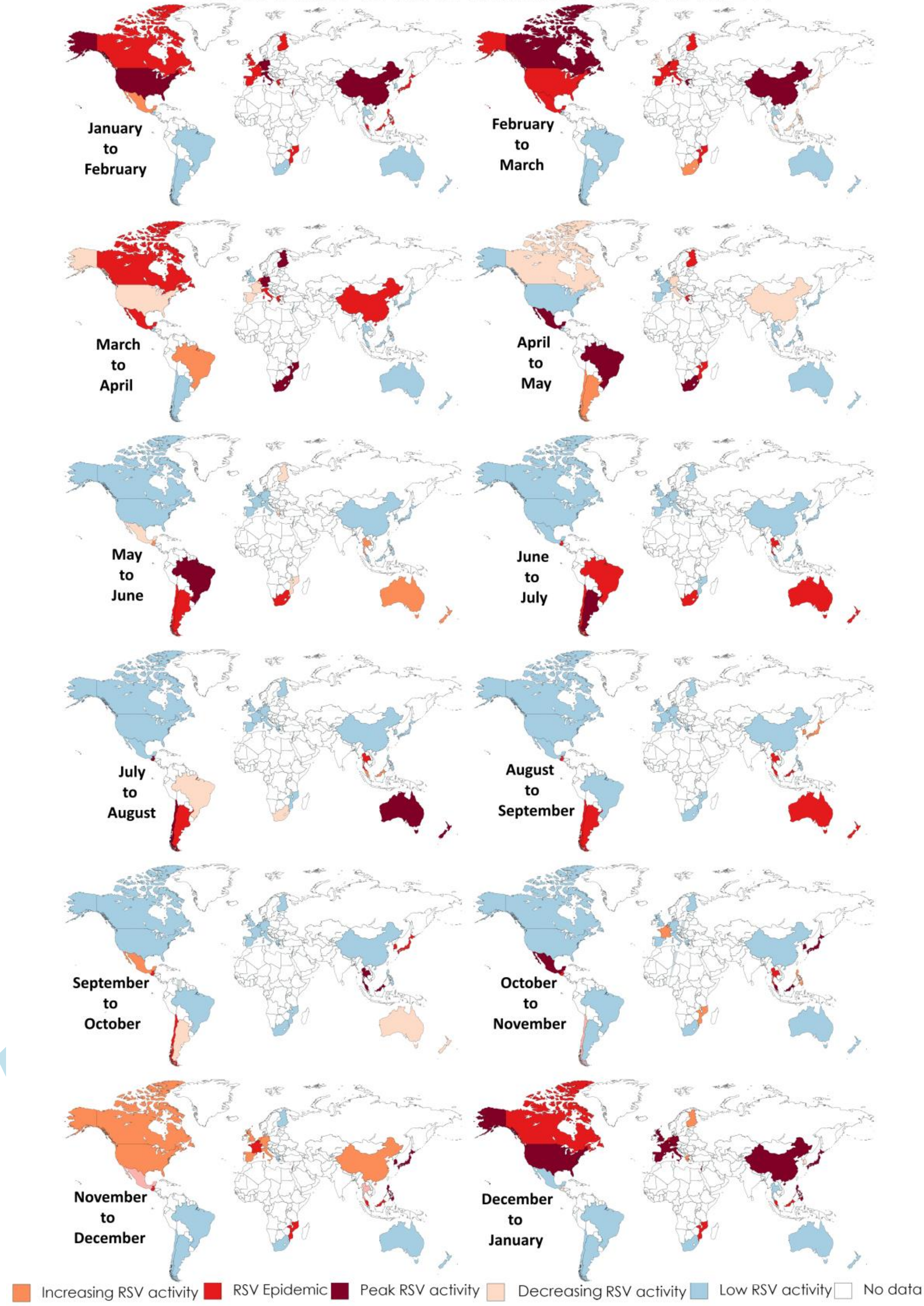

Figure 2. Country-specific RSV epidemiology. Some countries have more than one peak month as RSV shows high activity in different months every season. RSV usually travels from the South to the North, starting in most countries in the Southern Hemisphere between March and June, and between September and December in the Northen Hemisphere. Humid countries have their seasonal wave during the rainy season.

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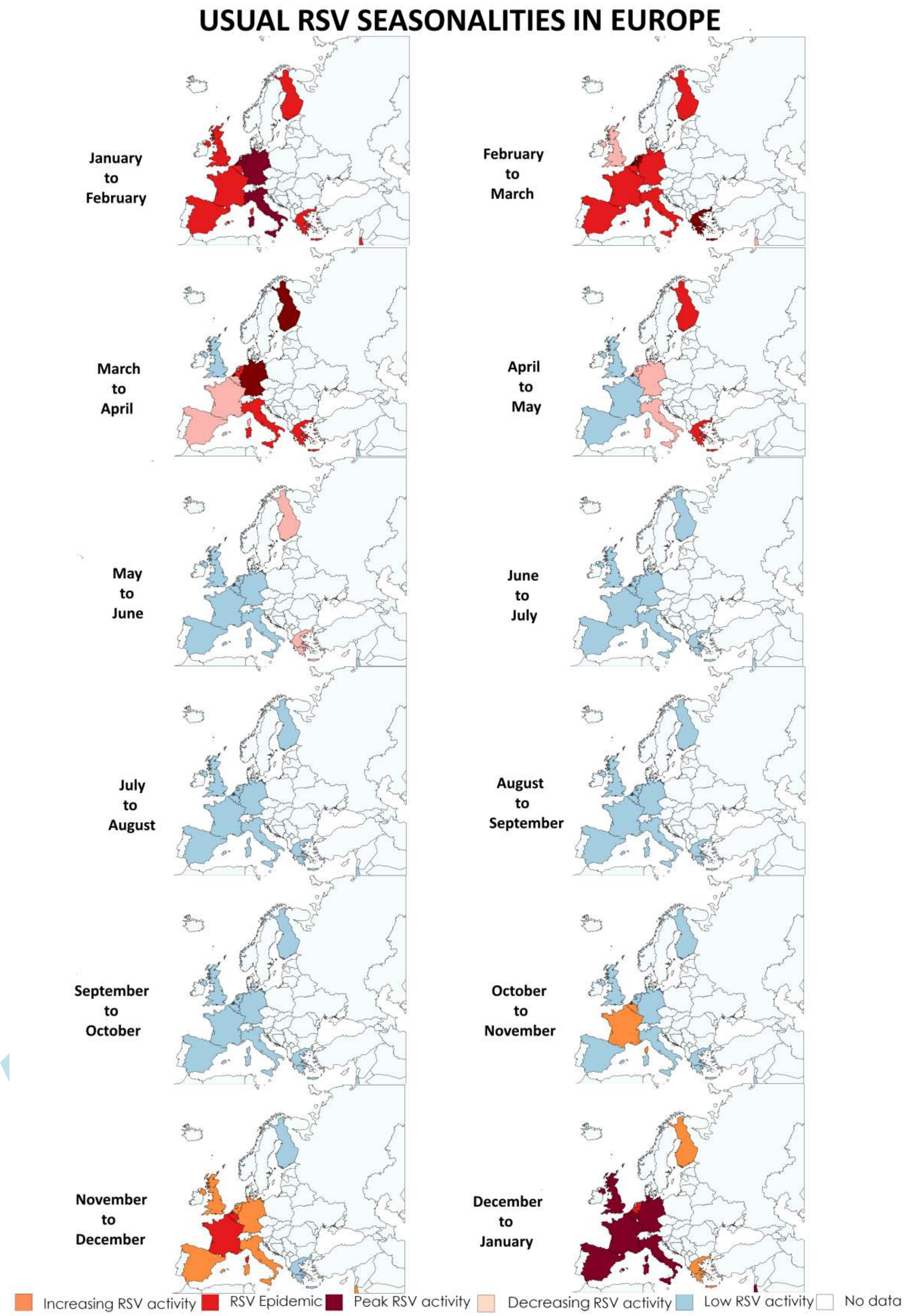

Figure 3. Country-specific RSV epidemiology in Europe. RSV usually travels from the South to the North and from the West to the East, showing activity in the continent from October to May in some countries. Peak activity is usually seen in winter for most of the countries, except for the most northern countries, where high activity is seen in the beginning of spring.

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