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Differential RSV seasonal patterns and meteorological factors in Florida, Puerto Rico and other US regions

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Title: Differential RSV seasonal patterns and meteorological factors in Florida, Puerto Rico and other US regions

Background: Respiratory syncytial virus (RSV) circulates in most areas of the US primarily during November to April. Florida, particularly the southeast area, has exhibited a unique pattern of RSV circulation with earlier onset and longer duration. Similarly prolonged RSV circulation has been observed in Puerto Rico. RSV circulation was assessed in Florida, Puerto Rico, and the rest of the US using the National Respiratory and Enteric Viruses Surveillance System (NREVSS). Additionally, RSV occurrence was examined for association with weather data that included temperature, humidity ad precipitation variables, using data from Weather Underground and National Oceanic and Atmospheric Administration (NOAA).

Methods: NREVSS weekly data was submitted from laboratories in the 50 states (2011-2013) and Puerto Rico (2011-2013). The number and percentage of specimens RSV-positive by antigen detection were used for consistency across geographic areas and years. RSV onset (first of 2 consecutive weeks with $\geq$10% RSV-positives) and offset (last of 2 consecutive weeks with <10% RSV-positives) defined RSV periods of increased seasonal epidemic activity, which were compared between southeast Florida, the rest of Florida, Puerto Rico, and the rest of the US. Weather stations were used to identify meteorological data for Southeast Florida region and Puerto Rico region. In order to assess whether the percent positive of RSV peak, which indicates the severity of the RSV season was associated with the peaks in temperature, humidity and precipitation, Poisson regression analysis was performed.

Results: From 2011-2013, 517 laboratories (including 3 in Puerto Rico; 11 in southeast Florida) reported ~740,000 RSV antigen tests to NREVSS, of which 13% were RSV-positive. Puerto Rico remained $\geq$10% RSV-positive for all months and closely paralleled the timing and shape of the RSV curve in southeast Florida, which had RSV onset during June-July compared to November for the rest of the US. RSV activity peaked earlier for southeast Florida and Puerto Rico (September-October), followed by the rest of Florida (November-December), and then the rest of the US (January-February). Poisson analysis reveled a positive correlation between RSV peaks and both temperature and humidity in the Puerto Rico region and a positive correlation between RSV peaks and temperature and precipitation in the Southeast Florida region.

Conclusions: RSV increased activity occurred months earlier in southeast Florida and Puerto Rico compared to the rest of the US, suggesting that factors uniquely common to southeast Florida and Puerto Rico might contribute to their seasonality, which has implications for timing of RSV interventions. Temperature and humidity were significantly associated with the peaks in RSV in the regions with tropical weather.

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Table of Contents

Introduction

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a common disease cause of infants and young children that is associated with substantial morbidity. It is the most important viral respiratory pathogen of early life (1) that infects the lungs and breathing passages. RSV can lead to serious illness in children under 12 months of age or younger and in adults over 65 years of age with weak immune systems. RSV is a viral respiratory pathogen that regularly produces an important outbreak each year and due to its strain variability, reinfection is common. By two years of age, 99% of children will experience at least one RSV infection and 50% of them will experience at least two RSV infections (2). Outbreaks may vary in length and season depending on the geographical region. Throughout most of the US, outbreaks typically last an average of five to six months (November-April), although there are regions where year-round epidemics have been reported. In tropical climates the patterns of RSV infection is less predictable and may occur throughout the year.

Seasonality

During 19987-2006, an estimated 132,000-172,000 children aged <5 years were hospitalized for RSV infection annually in United States (3). In temperate climate zones, RSV generally circulates during the fall, winter and spring (4), but the exact timing and duration of RSV seasons vary by region and year. In the United States RSV epidemics recur annually at regular, predictable intervals (5). In the northernmost regions of the United States (e.g. Rochester, NY), the peak incidence of disease is observed during the colder, winter months between December and March. In Washington, DC and in Chapel Hill, NC, epidemics alternate between long and short cycles, with peak disease occurring in either winter or spring. However, in the southeastern portion of the United States, RSV epidemics start earlier, in October and end earlier than in the north. In Florida and parts of Tennessee, RSV is present almost year round, being reported for 7 to 9 months of the year, with winter peaks similar to that observed in regions around

the equator (5). RSV hospitalization has become the common denominator by which to compare the impact of RSV disease on the child, the community and the economy. RSV hospitalization has become, the basis for determining severity of illness and impact of either preventive or therapeutic interventions on the infection. It remains the decisive indicator of RSV severity (6).

Prevention

Although no vaccine is currently available for protection against RSV infection, immunoprophylaxis in the form of a monoclonal antibody, palivizumab, has been shown to reduce hospitalizations among certain high-risk pediatric populations (7). The American Academy of Pediatrics recommends initiation and termination of immunoprophylaxis based on seasonal patterns of RSV circulation which may vary geographically (8).

RSV Trends in Southeast Florida

Southeast Florida is known to generally experience earlier and longer seasonal epidemics when compared with other parts of the country. Data from Florida has been traditionally used to determine and implement local seasonality, and thus to administer immunoprophylaxis for high-risk patients. Based on previous research, children in Southeast Florida who are considered at risk for severe RSV disease may not receive adequate prophylaxis with palivizumab if dosed according to the current policy statement issued by the Committee on Infectious Diseases of the American Academy of Pediatrics (9). Decisions on administration of palivizumab for RSV prophylaxis in high-risk children should ideally be based on results of local RSV test detection data (10).

Surveillance

Centers for Disease Control and Prevention (CDC) uses a passive surveillance system called the National Respiratory and Enteric Virus Surveillance System (NREVSS), to which labs and hospitals voluntarily report that provides data on the circulation of various viral pathogens in the United States, including RSV (11). It monitors RSV activity weekly nationwide and issues regional reports with the United States divided into 4 major zones- West, East, South and Central.

RSV activity in Tropical Regions

Past research has provided potential explanation for the long RSV season observed in Florida, suggesting that RSV activity is substantial in tropical areas when both ambient temperatures and humidity are high. Prolonged seasons also have been observed in other tropical areas such as Cuba and Puerto Rico. Other theories suggested as the factors for the changes in beginnings of the RSV season in these areas are immunity or crowding, or a slight shift in the age of the infected population (12).

Several hypotheses have been posited to explain the seasonality of RSV, although no single factor is sufficient to explain the diversity of seasonal patterns globally (13). Possible suggestions include seasonal changes in virus survival and transmissibility, host physiology and social behavior, and their interactions (13).

Purpose of this study

The primary objective of this study was to examine whether meteorological factors such as temperature, humidity and precipitation are significantly associated with the earlier RSV season in Southeast Florida and Puerto Rico. This work will differ from the previous analyses done on RSV in that it focuses on the factors uniquely common to Southeast Florida and Puerto Rico, which has implications for timing of RSV interventions. It would be useful to evaluate the postulated mechanisms driving seasonality and guide public health strategies nationally. The strength of this study are substantial, including data from consistent surveillance, population at national-level, and laboratory testing that gives uncommon ability to look at pathogen-specific incidence over time.

Estimates of relative contributions of meteorological factors are essential for a timely and effective implementation of preventive interventions and optimal treatment routines, especially in light of recent efforts at vaccine development for other respiratory diseases, as well as the goal of reducing child mortality by two-thirds between 1990 and 2015.

Methods

IRB approval was exempted for this research by CDC because the NREVSS did not contain any personal identifiers.

Study Population

This study is a secondary analysis of a de-identified data set from CDC's surveillance system called NREVSS, which monitors temporal and geographic patterns associated with the detection of respiratory syncytial virus (RSV). NRVESS is a laboratory-based passive surveillance system that monitors temporal and geographic patterns associated with the detection of respiratory syncytial virus, human parainfluenza virus, respiratory and enteric adenoviruses and rotavirus (14). Data are reported from university and community hospital laboratories, public health laboratories and commercial laboratories. The participating laboratories report virus antigen detections, isolations by culture and polymerase chain reaction (PCR) results on a weekly basis. Data collected includes the number of tests performed and the number of positive results each week for each test type. This system reports seasonal and geographical trends and records the number of specimens tested for RSV and number of positive tests detailed by week. CDC asks that labs report detections of respiratory viruses from respiratory specimens and detections of enteric viruses from enteric specimens online. Multiple specimens from the same patient may be reported, and reports are collected each week by noon on Tuesday. However, NREVSS do not collect any kinds of demographic characteristics or clinical characteristics such as age, sex, residents, clinical outcomes or symptoms for the ease of reporting, since the goal is to collect data on circulations of the various pathogens around the country.

Data Entry

When reporting to NREVSS, each lab has its own log account that they could access, and their data is entered in an Online Data Submission System (ODSS). Data that they enter in ODSS is automatically stored in a centralized SQL server, and NREVSS coordinators access the data through

Microsoft Access. The NREVSS reporting weeks goes from Sunday to Saturday and season runs from the first week of July to the last week of June the following year. Reporting labs are able to edit data for current and past seasons. The data validation feature can be used to optimize the accuracy of the data submitted to NREVSS. Validation can be performed as often as the laboratory wishes, but CDC asks that data be validated at least once every July to ensure the accuracy of the data submitted in the preceding NREVSS reporting season. To determine seasonal trends in the circulation of RSV at national regional levels, data collected by the NREVSS were analyzed.

Florida Department of Public Health

The Florida Department of Health (FDH) initiated its own statewide voluntary surveillance network in October 1999 to capture weekly RSV data from various regions of the state (north, central, southwest, southeast followed by northwest in January 2000) throughout the year (15). It was implemented to support clinical decision-making for prophylaxis of premature infants. Each participating laboratory submitted weekly aggregated numbers of tests performed and total number of positive tests to the Bureau of Epidemiology via mail or fax. The number of laboratories reporting data has varied over time and has generally included more than 12 total sites per year. Regional and statewide data are tabulated and posted to the FDH Web site, and are available for public health professionals, health care providers and public to view. The FDH collects weekly RSV data throughout the year from more than a dozen strategically located virology laboratories within 5 regions of the state (southeastern, central, southwestern, northwestern, and northern regions).

Data Analysis: Calculating the severity of the RSV season

In order to calculate the percent positives of given week by geographic area and by the whole nation, RSV test data and the number of positive results were assessed over a 2-year time period (2011-2013). RSV onset (first of 2 consecutive weeks with $\geq$ 10% RSV-positives) and offset (last of 2 consecutive weeks with <10% RSV-positives) defined periods of increased seasonal epidemic activity,

which were compared between Southeast Florida, the rest of Florida, Puerto Rico, and the rest of the US. The location of the laboratory was used to define the geographic area studied.

Weather Underground

Weather Underground (www.wunderground.com) is a commercial weather service that provides real-time weather information via the Internet (16). Weather Underground provides weather reports for most major cities across the world on its website, as well as local weather reports for newspapers and Web sites. Most of its United States information comes from the National Weather Service (NWS), as information from that agency is within the public domain by federal law. Based in Ann Arbor, Michigan, it was founded in 1995 as an offshoot of the University of Michigan's Internet weather database. It regularly collects data from a large number of weather stations. In addition, National Climatic Data Center (www.ncdc.noaa.gov) was used in order to identify weather station IDs.

National Oceanic and Atmospheric Administration (NOAA)

The National Oceanic and Atmospheric Administration is a scientific agency within the United States Department of Commerce focused on the conditions of the oceans and the atmosphere. Climate Data Online (CDO), which provides free access to NCDC's archive of historical weather and climate data in addition to station history information, was used in order to identify weather stations that were not available in the Weather Underground website. The data extracted from NOAA included quality controlled daily, monthly, seasonal, and yearly measurements of temperature, precipitation, wind, and degree days as well as radar data.

Selecting Weather Stations

For both Southeast Florida and Puerto Rico regions, weather stations were selected that were closest to each of the laboratories that reported to NREVSS. The weather stations were searched by zip

code of the corresponding laboratories, and one weather station was selected per lab. Weather station IDs were used to identify each station.

Then, weather station history files were downloaded for each of the stations. The list of variables in each of the files included date, temperature, humidity, precipitation, dew point, wind and sea level pressure. The files were then exported into SAS. For this particular research, only 3 variables were used- temperature, humidity and precipitation. Each of the separate files was merged into SAS for analysis. All analysis was performed in Microsoft Excel, Microsoft Access and SAS 9.3.

The merged SAS files were then exported into Excel in order to combine variables with the RSV data from NREVSS. The weather station IDs were matched to NREVSS ID and the dates used in Weather Underground were matched with NREVSS dates. In the Excel file, RSV detections, mean temperature, mean humidity and mean precipitation were recorded for each of the labs per week.

Data Analysis: Poisson Regression

In order to calculate the percent positives of given week, the Number of Positive RSV tests was divided by the total number of RSV tests and was multiplied by a 100. To assess whether the percent positive of RSV peak, which indicates the severity of the RSV season, correlates with the peaks in temperature, humidity and precipitation, Poisson regression analysis was performed. Meteorological data from two separate groups were analyzed, which were Southeast Florida region and Puerto Rico region. In order to generate general statistics on precipitation, temperature, RSV tests performed and detections, summary statistics was assessed using SAS. After reviewing differences, Poisson regression analysis was performed with data set containing the combined variables from weather data and RSV data from NREVSS. Lastly, Goodness of Fit test was used to determine how well the model fit the data.

Results

Descriptive Statistics

From 2011 to 2012, 526 labs reported to NREVSS and the number of tests performed was 574,101 (Tables 1-2). The number of tests reported positive for RSV was 70457 (12.3%). From 2012 to 2013, there was a slight decrease in the number of labs that reported to NREVSS. A total of 517 labs participated, that performed 736727 tests and 95743 positives results were reported, yielding a 12.3% percent positive RSV tests for this season. From 2012 to 2013, although there were some variations in the number of labs, number of tests performed, number of positives, and the percent positive or RSV remained consistent from season to season.

Next, average values and range of the temperature and humidity and the total amount of precipitation and range were assessed by geographic area (Table 3). Southeast Florida and Puerto Rico experienced higher average temperature compared to the rest of Florida region, which excluded the Southeast region. Average humidity values were consistent among the three different regions. Since precipitation amount fluctuated significantly within the season, total amount was measured instead of average values. Southeast Florida experienced a markedly higher amount of precipitation, compared with the rest of the country (Table 3).

Percentage of positive antigen tests for RSV by geographic areas in the US reported to NREVSS from 2011-2013 season was graphed (Figure 1). Figure 1 shows that increased RSV activity occurred months earlier in southeast Florida and Puerto Rico compared to the rest of the US. This result shows that factors uniquely common to southeast Florida and Puerto Rico might contribute to their seasonality, which has implications for timing of RSV interventions.

Poisson Regression analysis results

Table 4 shows the analysis of maximum likelihood parameter estimates for the Puerto Rico region. The estimates show that there is a positive correlation between temperature, humidity and percent positive RSV. Precipitation was negatively correlated with percent positive RSV. However, p-values suggested that only temperature was significantly correlated with the peaks in percent positive RSV.

Table 5 shows results of the same analysis for the Southeast Florida region. In this region, both temperature and precipitation were positively correlated with percent positive RSV, and humidity showed a negative correlation. P-values suggested that both temperature and humidity were significantly correlated with peaks in RSV.

Table 6 shows the Goodness of Fit results of the models for both Puerto Rico and Southeast Florida regions. The p-values obtained for both regions indicated that the model was a good fit for the data.

Table 1. Number of laboratories reporting to NRVESS, number of tests and number of positive tests by season from 2011-12 season to 2012-13 season.

Season	Number of Labs	Number of Tests	Number of positives
2011-2012	526	574101	70457
2012-2013	517	736727	95743

Table 2. Number of laboratories reporting to NRVESS, number of tests and number of positive tests by geographic area from 2011-12 season to 2012-13 season.

Geographic area	Number of Labs	Number of Tests	Number of positives
US (excluding Florida and Puerto Rico)	498	1202243	149886
Florida (excluding Southeast Florida)	25	55502	7022
Southeast Florida	11	37744	4716
Puerto Rico	3	15339	4576

Table 3. Average temperature, humidity and precipitation of five Florida regions and Puerto Rico from June 2011 to July 2013.

	Mean (Range)		Total (Range)
Geographic area	**Temperature**	**Humidity**	**Precipitation**
Southeast Florida	76.44 (53-89)	71.86 (51.91-87.90)	572.13 (0-10.58)
Florida (excluding Southeast Florida)	73.58 (49.28-87.14)	73.97 (49.43-89.29)	249.49 (0-13.44)
Puerto Rico	76.17 (75.86-86.57)	73.77 (63.14-81)	159.66 (0-12.96)

Table 4. Analysis of Maximum Likelihood Parameter Estimates for Puerto Rico region

	Degrees of Freedom	Estimate	Standard Error	95% Confidence Interval	p-value
Intercept	1	-9.1799	0.9732	(-11.08, -7.27)	<0.0001
Mean Temperature	1	0.1478	0.0086	(0.0089,0.13)	<0.0001
Mean Humidity	1	0.0008	0.0061	(0.0061, -0.011)	0.8957
Mean Precipitation	1	-0.0033	0.0128	(-0.029, 0.0022)	0.7948

$$\mathbf{Log}\,(\boldsymbol{\mu}) = -\mathbf{9.1799} + \mathbf{0.1478}(\boldsymbol{x1}) + \mathbf{0.0008}(\boldsymbol{x2}) - \mathbf{0.0033}(\boldsymbol{x3})$$

Table 5. Analysis of Maximum Likelihood Parameter Estimates for Southeast Florida region

	Degrees of Freedom	Estimate	Standard Error	95% Confidence Interval	p-value
Intercept	1	0.182	0.2922	(-0.39, 0.75)	0.5333
Mean Temperature	1	0.045	0.0035	(0.038, 0.052)	<0.0001
Mean Humidity	1	-0.0214	0.0033	(-0.028, -0.015)	<0.0001
Mean Precipitation	1	0.0084	0.0109	(-0.013, 0.030)	0.4394

$$\mathbf{Log}\,(\boldsymbol{\mu}) = \mathbf{0.182} + \mathbf{0.045}(\boldsymbol{x1}) - \mathbf{0.0214}(\boldsymbol{x2}) + \mathbf{0.0084}(\boldsymbol{x3})$$

Table 6. Goodness of fit results for Southeast Florida and Puerto Rico regions

	Degrees of Freedom	Chi Square	p-value
Southeast Florida	385	525	<0.0001
Puerto Rico	106	210	<0.0001

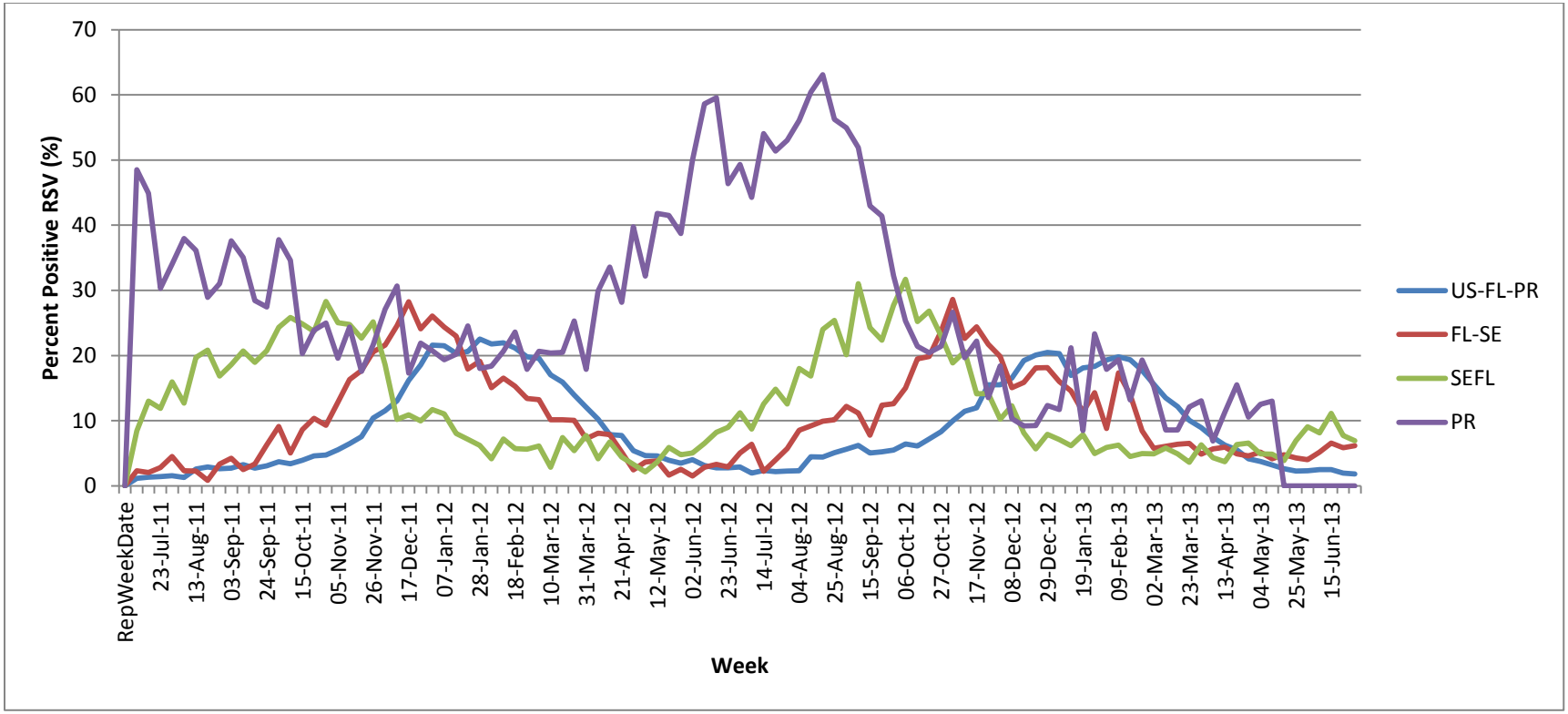

Figure 1. Percentage of positive antigen tests for RSV by selected geographic areas in the United States reported to NREVSS from 2011-12 season to 2012-13 season. (US-FL-PR: US excluding Florida and Puerto Rico, FL-SE: Florida excluding Southeast region, SEFL: Southeast Florida, PR: Puerto Rico)

Discussion

Public health importance

High-risk populations exposed to RSV infection are susceptible to develop severe and fatal disease as well as long-term disability (17). This review combining literature and electronic data sources, suggested that a large fraction of tropical locations experience focused seasons of RSV activity and that the peak period varies from year to year (18).

In examining variables for both Southeast Florida and Puerto Rico regions, both temperature and humidity were found as a common variable in those two regions to have significant relationships to peaks in percent positive RSVs. It is highly important that these variables have significant relationships because they could be used as a determining factor for administration of prophylaxis in the regions that experience earlier onset of RSV transmission. The current policy statement offered by the American Academy of Pediatrics for the prophylaxis of RSV recommends that palivizumab should be administered to high-risk children in a series of 5 monthly injections beginning in November and concluding in March (21). Based on the findings of this study, children in Southeast Florida and Puerto Rico regions who are considered at risk for severe RSV diseases may not receive adequate prophylaxis with palivizumab if dosed according to the current policy statement issued by the Committee on Infectious Disease of the American Academy of Pediatrics (22). It would be best that the decisions on administration should be based on the results of local RSV test detection data. It is hoped that this study will provide assistance in achieving the goal.

Strengths of this study

The strengths included consistent surveillance, and laboratory testing that gives the investigators the uncommon ability to look at pathogen-specific incidence over time. The study adds data and rigorous methods to what has been a largely speculative explanation for many years– people are more susceptible to the transmission of RSV in tropical regions. This study combines both Southeast Florida and Puerto Rico regions, which adds more data in the comparison group. In addition, the study is significant because

it acts as a quantitative study to systematically review RSV seasonal patterns on a national scale. Due to strengthened respiratory virus surveillance in recent years, seasonality information was available for 1,043 laboratories (from 2011 to 2013), with 14 laboratories representing the tropics.

Limitations of this study

The shortcomings to this study were that the NREVSS data did not contain any demographic data, such as age, sex and clinical information including the severity of the RSV infection. Therefore, it was insufficient to support hypotheses from previous literatures that climate, summer travel patterns, and family size may be factors contributing to increased person-to-person RSV transmission among populations in the tropical regions. In addition, some of the data were reported from laboratories of Children's hospitals while others were reported from laboratories of general hospitals. Many of the children's hospitals that report to NREVSS were located in Southeast Florida regions. This could have acted as a confounder because data from children's hospitals have higher chance to reporting higher number of percent positive RSV data, which might make seem that there is a higher RSV activity in that region. It could have been confirmed by stratifying the results by the type of hospitals, but the sample size was too small to accomplish this. In addition, much of the available information on RSV seasonality in tropical countries such as Puerto Rico has been accumulated in just the past 3 years. For matching weather data used with the RSV data on NREVSS, information was only available from two weather sources and the results from them might have been biased due to small sample size.

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