The seasonal variations of respiratory syncytial virus infections in Turkey: a 2-year epidemiological study

Turkish Neonatal Society

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Respiratory syncytial virus (RSV) infections may cause severe respiratory diseases, particularly in infants and young children. In order to determine the timing of prophylaxis, the seasonal variations of RSV had to be determined. We report the climate-related results of an epidemiological study conducted in 32 hospitals of Turkey between May 2008 and September 2010, on children <2 years of age hospitalized with lower respiratory tract infection. Information on socio-demographics, medical history, risk factors for RSV, diagnosis and severity of RSV, and hospitalization was recorded. RSV Respi-strip test kits were used to detect RSV. The meteorological data, including average monthly temperature, relative humidity (RH) and rainfalls of all cities were obtained, and the correlations between meteorological variables and RSV positivity were determined. Informed consents were obtained before the study. Overall, 3,464 children (61.9% boys), with a mean age of 6.4 months, were evaluated. RSV positivity was 16.9%. RSV peaked in January and March, in the first and second RSV seasons, respectively. When Turkey was evaluated as a whole, RSV was positively correlated with RH ($p<0.001$, $R=0.627$) and rainfalls ($p=0.001$, $R=0.572$), and was negatively correlated with temperature ($p<0.001$, $R=-0.778$). However, when the regions were evaluated separately, the rainfalls had a negative correlation with RSV activity in the Black Sea and East Anatolian regions. The current study shows the seasonal variation of RSV infections in Turkey in two consecutive RSV seasons. Country-specific viral surveillance systems are required to detect respiratory virus activities and to implement health care strategies.

Key words: seasonality, children, epidemiology, Turkey, respiratory syncytial virus infections.

Respiratory syncytial virus (RSV) infections are among the leading causes of severe respiratory illness and hospitalization of infants and young children worldwide[1,2]. RSV infections comprise 20% of lower respiratory tract infections, and the global RSV disease burden is estimated as 64 million cases and 160,000 deaths annually, with most of the deaths occurring in the developing countries[3,4].

Nearly all children by 24 months of age have been infected at least once with RSV, and about half have experienced two infections[5,6]. Medical risk factors such as preterm birth, cardiac diseases or chronic lung disease increase the severity of RSV infections, leading to longer periods of hospitalization and increased cost[1,4,7,8]. Children who experience RSV infection early in life run a high risk of subsequent recurrent wheezing and asthma, especially high-risk infants, for whom prophylaxis with anti-RSV monoclonal antibodies such as palivizumab is highly recommended[9]. However, palivizumab treatment is relatively expensive and, in order to optimize treatment strategies in RSV infections, cost-effective strategies are needed.

The seasonal variations of respiratory virus diseases, particularly the variations in influenza epidemics, have been extensively studied. Because of the high hospitalization rates and mortality due to RSV, RSV seasonality has attracted the attention of investigators especially in the last 30 years. Reports from various countries throughout the world, particularly from developed countries, have

shown a variation in the number of RSV cases according to meteorological variables. Studies revealed that the seasonality of RSV disease differed according to the location of the country with respect to the equator, in addition to the personal, behavioral and immunological characteristics of the patients.

Turkey, the Eurasian country, located in the Southeastern part of Europe and the Southwestern part of Asia, has the geographic coordinates of 39°00'N latitude and 35°00'E longitude, similar to countries like Greece and Italy. The climate is generally temperate, but there are variations among the regions of Turkey, which is surrounded by the Aegean Sea, Black Sea and Mediterranean Sea, and has both coastal and inner regions.

To our knowledge, no large-scale studies have been conducted to date on the seasonal variations of respiratory virus infections in this region of the world.

In the present study, we report the climate-related results of an epidemiological study conducted in Turkey on children <2 years of age hospitalized with the diagnosis of lower respiratory tract infection. We evaluated the correlations of meteorological variables with RSV positivity in Turkey, as well as among the geographic regions.

Material and Methods

The present prospective epidemiological study was conducted in children <2 years of age who were hospitalized with the diagnosis of respiratory failure due to acute lower respiratory tract infection (bronchiolitis or pneumonia) in 32 hospitals, between May 2008 and September 2010, throughout Turkey. Children who had used palivizumab against RSV infection, and the cases in whom respiratory samples could not be collected in 24 hours after hospitalization or in 24 hours after emergency room (ER) or outpatient clinic administration were excluded from the study. Children with immune deficiency, cystic fibrosis, or congenital or acquired disorders affecting the respiratory system were also excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki. Ethics Committee approvals were obtained from all participating centers. Informed consents were obtained from the relatives or legal representatives of the children before any study procedure was conducted. All of the participating centers were required to enroll subjects and collect samples for 24 months. Sociodemographic information, medical history and risk factors for RSV infection were recorded for each patient on a case report form before the physical examination.

In order to detect RSV, nasal-washing samples, nasopharyngeal aspirates, or nasal or nasopharyngeal swabs were collected from each child. RSV Respi-strip test kits (Coris Bioconcept, Belgium), provided by the Turkish Neonatal Society, were used to detect RSV in the samples. The principle of this point-of-care test is that a nitrocellulose membrane is sensitized with a monoclonal antibody directed against RSV while a mobile anti-RSV monoclonal antibody is conjugated to colloidal gold particles. If the sample contains RSV, conjugate RSV complex binds to the anti-RSV antibody, revealing a red line on the test strip. Testing was performed in accordance with the manufacturer's instructions. In the literature, the sensitivity and the specificity of RSV Respi-strip test was found to be 92% and 98%, respectively, and the diagnostic efficacy was 95%[10]. The obtained samples were tested immediately or stored at 2-8°C for 24 hours or at -20°C for longer periods, if required.

The diagnosis, severity of the disease and the information regarding hospitalization were also recorded.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 15.0; SPSS Inc., Chicago, IL, USA). The meteorological data, including average monthly temperature in Celsius degrees (°C), average monthly relative humidity (RH) in percentages, and average monthly rainfalls in millimeters of all cities were obtained from the Turkish State Meteorological Service. These data were used to calculate the monthly average values of the regions and of Turkey as a whole. The number of RSV-positive cases each month was expressed in terms of the percentage of children hospitalized with a lower respiratory tract infection during the month. We chose to analyze the data monthly, since monthly

data describes trends and seasonality more accurately.

According to climate characteristics, we analyzed the correlation between meteorological variables and RSV positivity in four regions as follows: the Marmara, Mediterranean and Aegean region, Black Sea region, East Anatolian region, and Middle Anatolian region. As the Black Sea region has high rainfalls continuously throughout the year, it was analyzed separately from the other coastal regions, while the inner regions, the East Anatolian and Middle Anatolian regions, were analyzed separately due to their different climate characteristics, with the Middle Anatolian region being warmer than the East Anatolian region.

Descriptive analysis was presented as mean, standard deviation, and minimum and maximum values. The relation of RSV infections with age groups and sex was evaluated using the chi-square test. All correlations were tested by the Spearman correlation test. A p value <0.01 was considered significant. We calculated that a sample size of 3,464 produces a two-sided 95% confidence interval with a width equal to 0.025 when the sample proportion was 16.9%.

Results

During the study period, 3,464 children (61.9% boys), with a mean age of 6.4 months (range 0 - 24 months), were included in the study. The distribution of the children according to age groups was as follows: 37.5% in 0-3 months, 13.7% in 3-5 months, 17.6% in 5-8 months, 14.9% in 8-12 months, and 16.3% in the 12-24 months.

Respiratory syncytial virus (RSV) positivity was 16.9% (585 patients) in all collected samples. Most of the positive results were obtained in children aged 0-8 months, and the highest positivity rate was among children aged 0-3 months (27.4%; p<0.01) according to age groups. RSV positivity was the highest in the Black Sea region (21.9%), followed by the Aegean (21.5%) and the Central Anatolian (17.9%) regions of Turkey.

When Turkey was evaluated as a whole, in the first RSV season, RSV activity onset was in October, reached its peak in January, and descended in April. In the second season, the cases started to increase in October, peaked in March and descended until July. RSV activity was observed to have a biennial pattern; an early season with a strong activity was followed by a late season with a weak RSV activity.

When the association between RSV positivity and the meteorological variables was evaluated, it was observed that RSV was significantly positively correlated with RH (p<0.001, R=0.627) and rainfalls (p=0.001, R=0.572), and was negatively correlated with temperature (p<0.001, R=-0.778) (Fig. 1).

There was a positive correlation between RSV positivity and RH, and a negative correlation between RSV positivity and temperature in all regions. However, the rainfalls were positively correlated with RSV activity in all regions, except the Black Sea and East Anatolian regions (Table I).

Discussion

To our knowledge, this is the first study conducted on a large sample size of children <2 years of age, demonstrating the seasonal variations of RSV infections in two consecutive years in 32 centers in Turkey. RSV positivity was seen as 16.9% among all samples. Among 585 children with positive samples, the highest rates were observed among children aged 0-3 months (27.4%; p<0.01), similar to the study by Terletskaia-Ladwig et al.[11], the mostly affected and hospitalized population from lower respiratory tract infections[11,12].

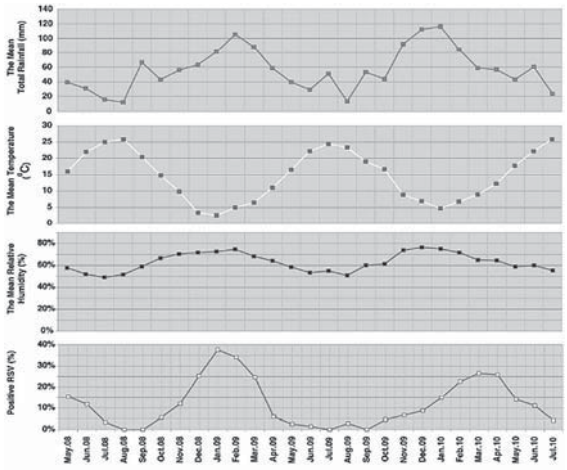

Figure 1. The seasonal patterns of RSV positivity according to meteorological variables across 32 sites in Turkey. Months in which less than 10 children were recruited are not presented.

Table I. Correlation between Respiratory Syncytial Virus (RSV) Positivity and Meteorological Variables in Regions of Turkey

	RSV Positivity							
	Mediterranean, Aegean, Marmara		Black Sea		Middle Anatolian		Eastern Anatolian	
	r	p	r	p	r	p	r	p
Relative humidity (%)	0.647	<0.001	0.55	0.001	0.649	<0.001	0.579	0.001
Temperature	-0.825	<0.001	-0.637	<0.001	-0.699	<0.001	-0.554	0.001
Rainfalls	0.627	<0.001	0.22	0.135	0.643	<0.001	0.299	0.065

Until today, the seasonal variations of RSV infections have been widely investigated in various studies, and it has been observed that RSV epidemics depend on the climate and geographical location of the country, the spread and the antigenicity of the virus, and the behavioral factors and cyclic changes in the immunological susceptibility of the individuals.

In temperate climates, RSV cases tended to peak in winter[9]. In tropical or subtropical climates, RSV has been determined to have two different patterns; in countries north of the equator, the RSV peak correlates with low temperatures and high rainfall, while in countries south of the equator, RSV correlates with low temperatures and low rainfall. In the equator, RSV is observed year around, prevalent for 7-8 months[4]. This profile suggests that temperature is not the only meteorological variable affecting RSV epidemics.

Respiratory syncytial virus (RSV) infection is believed to be transmitted via two routes: by large particle aerosols and by direct contact with RSV in solutions of human secretions. A fall in environmental temperatures even modestly below room temperature have been found to prolong the stability of RSV in secretions on fomites, if reasonable humidity was maintained. Indeed, it was reported that a minor decrease in temperature leads to an increase in the monthly community-acquired pneumonia and RSV cases[13,14]. When aerosols were maintained for periods of 1-61 minutes, RSV became more stable at 40% humidity. When both temperature and absolute humidity are high, RSV activity is substantial, showing greater stability in aerosols[15]. Ultraviolet B (UVB) radiation may inactivate the virus in the environment or influence susceptibility to RSV by altering host resistance, stimulating vitamin D metabolism[9].

It has also been reported that peaks in RSV activity were related to temperature in a bimodal fashion, with peaks above temperatures 24-30°C and below 2-6°C, and a RH of 45-65%. At sites with persistently warm temperatures and high humidity, RSV activity showed continuous peaking in summer and autumn[9,15]. In areas where temperatures remained cold throughout the year, RSV activity again became continuous[15].

In tropical and subtropical climates, high humidity and stable high temperatures enable RSV to be sustained in large particle aerosols, to permit year-round transmission. Since maximal rainfall and temperatures are seen in summer months, RSV tends to correlate with temperature and humidity. However, drier weather may inactivate RSV[9]. RSV activity was reported to be observed throughout the year in Taiwan, situated on an island, with a subtropical climate, without significant seasonality. The mean temperature difference was only 8°C and the effect of rainfall was not evident[2]. In a study conducted in Hong Kong, which also showed a subtropical climate, RSV was associated with high temperatures and high rainfalls (higher environmental RH) [16]. A study from Mexico reported that temperature, inversely correlated with RSV activity, was found to be among the variables explaining year-to-year variability in RSV activity[12]. A study in a tropical region, Salvador, Brazil, has also reported an inverse correlation with ambient temperature and a direct correlation with precipitation, with RSV peaks observed in April, May and June[14].

The laboratory data from 11 regions in two consecutive years in the United States revealed that the onset of RSV infections occurred late in the fall, and season offset in all regions with temperate climates occurred in mid-February-mid April. However, in Florida, having a humid

subtropical climate, the onset was in mid-July, and the RSV season had a longer duration[17].

In temperate climates, RSV activity becomes prominent in winter, correlating with lower temperatures. In these climates, summertime RSV would only be seen in areas with very high rainfalls and warm temperatures[9]. In arid regions with low temperatures, aerosol transmission is terminated by low humidity, and RSV infections transmit with solutions of human secretions.

In an Italian study, evaluating the RSV rates in children ≤4 years of age, in two periods, the RSV peak was observed in February in the first year (31.6%) and in March (19.2%) in the second year. It was observed that the study population consisted mostly of children at lower ages in the first year[18]. In a prospective epidemiological study conducted in four regions, in seven pediatric hospitals from Greece, RSV incidence was 27% in 1998-1999, with a peak in January-February, and 37.7% in 1999-2000, with a peak in February-March[8]. However, meteorological variables were not evaluated in the two above-mentioned studies.

In a study conducted in Spain, where a continental climate with low temperatures, high atmospheric pressure, low RH, and rainfalls exists, it was observed that RSV was associated with low temperatures and low absolute humidity, and with absolute humidity being independently correlated with RSV[19].

In a study reporting the results of 11 laboratories in the Netherlands, having a temperate, marine climate like in the United Kingdom, RSV activity was positively correlated with RH and negatively correlated with temperature[6].

Peaks of RSV infection have been observed to show a biannual pattern in temperate climates[4]. In a German study conducted between 2003 and 2006, RSV incidence was 19% and RSV was inversely correlated with temperature. RSV showed an annual or biannual pattern in this study[13]. Terletskaia-Ladwig et al.[11] reported that an early season with strong RSV activity was followed by a late season with weak activity, showing a biennial rhythm, like in Finland and Sweden in another German study.

In a study conducted in Croatia Zagreb, having a Mediterranean continental climate, RSV outbreaks were observed to show a biennial pattern. The cycles of the major epidemics were repeated at 23-25 months, followed by a minor epidemic after 14-16 months. While RSV directly correlated with humidity and inversely correlated with temperature at the major outbreaks, the number of RSV cases was only correlated inversely with humidity in the minor outbreaks[20].

To our knowledge, the relation between the seasonal variations and meteorological variables has not been evaluated in Turkey. Kanra et al.[21], in their multicenter study on high-risk patients <2 years of age, observed RSV frequency as 29.5% among high-risk infants between 2000 and 2002, and RSV peak occurred between January and April; however, the relation with the meteorological conditions was not evaluated[21].

In the present study, RSV peaks were observed in January and in March in the two subsequent RSV seasons. We observed that the RSV activity also showed a biennial pattern in Turkey, like in Germany, Croatia, Finland, and Sweden: an early season with strong RSV activity followed by a late season with weak activity. When the association between RSV positivity and meteorological variables was evaluated, similar to all countries with temperate climate, RSV was positively correlated with RH ($p<0.001$, $R=0.627$) and rainfalls ($p=0.001$, $R=0.572$) and negatively correlated with temperature ($p<0.001$, $R=-0.778$).

The Black Sea region and the East Anatolian region of Turkey have different climate characteristics when compared to the other regions. The Black Sea region is almost always rainy and the East Anatolian region is cold with a relatively lower humidity. Therefore, it was not surprising to determine that the effect of rainfalls on RSV activity in these two regions was less of a factor.

As was previously reported, only 15-40% of RSV infections were attributed to meteorological variables[22]. Crowding because of the opening of schools, holidays, and cold weather plus a suitable susceptible population of newborns may trigger the epidemic appearance of RSV[4]. The use of air conditioning, by lowering the temperature and RH, may enable the survival of RSV indoors[16]. In addition, immunological characteristics of the host as well as inherent genetic traits of the virus itself have an effect on the RSV activity[15].

RSV infections mostly endanger small children and infants, creating major morbidity by lower respiratory tract infections. It is particularly risky in high-risk patients, such as preterm children and children with an underlying medical condition. After the introduction of the RSV vaccine in the late 1960s, resulting in enhanced RSV disease and pulmonary eosinophilia, no vaccine against RSV infections has yet been developed. Therefore, prophylactic agents against RSV infections, i.e. palivizumab, must be administered to high-risk populations at the recommended periods before or at the beginning of the RSV season. Palivizumab is recommended to be given in monthly injections for five months[7,23]. For most infants, five monthly doses of palivizumab will provide >20 weeks of antibody levels, and should be sufficient for the whole RSV season. Antigen detection tests are valuable in diagnosing RSV infection; however, positive predictive value of the test decreases as disease incidence decreases, like at the onset and the end of the RSV season[23]. As seasonal patterns of RSV change among countries, and even among the regions of the same country, it is essential to obtain country-based information, particularly in countries where continuous viral surveillance is not carried out, in order to determine the public health policies.

The limitation of the present study is that, like every prospective study, the analysis was limited to the samples available for respiratory virus testing, not every individual who was infected by the virus. It is also important to understand our results pertain to infants hospitalized due to a lower respiratory tract infection, and rates of RSV are presented as the percentage of infants hospitalized due to a lower respiratory tract infection.

The current study shows the seasonal variation of RSV infections in Turkey in two consecutive RSV seasons. We believe that a viral surveillance system is required in all countries to detect the activity of respiratory viruses and to implement health care strategies.

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