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Seasonality of Infections Caused by Respiratory Viruses in Newborns and Their Relation to Meteorological Factors

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Abstract

Objectives – Most viral respiratory tract infections (VRTI) are seasonal diseases and frequently severely affect public health by causing seasonal epidemics and pandemics, also in newborns. The objective of this study was to analyse the relation of meteorological factors to the occurrence of neonatal VRTI and to estimate their predictive role for VRTI seasonality. **Patients and methods** – The retrospective observational cohort study enrolled 228 newborns (56% male and 29% preterm) aged up to 44 postmenstrual weeks, hospitalized due to acute VRTI between January 2015 and December 2020 in the central Slovenian region. The meteorological data for the same geographical region and time period were assessed, and correlation, multiple regression and cut-off values were analysed. **Results** – A typical seasonal distribution of VRTI from December to March was observed and the large majority of cases were due to respiratory syncytial virus (RSV) infection. Low air temperature, high relative humidity, shorter daily solar radiation and increased cloud cover were associated with an increased risk of neonatal, either RSV or non-RSV VRTI. **Conclusions** – Meteorological factors, particularly air temperature and relative humidity, were associated with neonatal VRTI occurrence in the temperate climate of central Slovenia. The average daily air temperature below 4.9 and 3.8 °C could predict the onset of the VRTI and RSV VRTI season, respectively. These factors could be used as real-time predictive warning, especially for RSV season onset and the need to begin RSV immunoprophylaxis in vulnerable newborns.

Key Words: Respiratory tract infections ▪ Newborn ▪ Respiratory syncytial virus ▪ Weather ▪ Climate.

Introduction

Most viral respiratory tract infections (VRTI) are seasonal diseases, occurring in close relation to meteorological changes, primarily by reducing the resistance of the human body to infection, and by affecting the ease with which infections spread (1). The seasonal occurrence of these infections frequently severely affects public health by causing epidemics and pandemics and transiently overloads health care systems.

Newborns are especially prone to VRTI and represent a group of infants at high risk for a severe course of these infections. In various climates, the most common pathogens in this age period are respiratory syncytial virus (RSV), human rhinovirus, influenza virus, parainfluenza virus, adenovirus, human metapneumovirus, human bocavirus and human coronavirus (2). All these viruses also cause the majority of VRTI cases in Slovenia, a central European country with a mainly continental climate (3–5). However, the most potent of all these is RSV, one of the most contagious human pathogens, which is responsible for a high burden of disease, especially in preterm infants and infants with chronic diseases (6). The annual seasonal RSV pattern in northern hemisphere temperate regions is predictably limited to 3–5 months, spanning from October/November to March/April, with peak incidence in January/February (7,8). To support the public health response, countries use different approaches to predict the beginning and end of the VRTI season. In Slovenia, passive RSV surveillance is performed by combining the national laboratory data and different calculation methods (9). On the basis of this surveillance, various preventive measures are taken, e.g. RSV infection immunoprophylaxis with humanized monoclonal antibodies for high-risk groups of newborns (10).

The present study investigates the seasonality of VRTI caused by RSV and other respiratory viruses in newborns and their relation to meteorological factors in the central Slovenian region. Comprehension of this relation, especially in vulnerable newborns, could well lead to more prompt and better adjusted strategies to reduce the incidence and burden of these infections during adverse meteorological conditions.

Patients and Methods

A retrospective observational cohort study enrolled 228 newborns (56% male and 29% preterm) aged up to 44 postmenstrual weeks, hospitalized due to acute VRTI in a tertiary referral hospital in the central Slovenian region between January 2015 and December 2020. The demographic, clinical and epidemiological characteristics of newborns were collected from their medical records. The viral aetiology of infection was confirmed after a nasopharyngeal swab or tracheal aspirate tested positive for respiratory viruses by PCR method.

The meteorological data from January 2015 to December 2020 were collected from the Slovenian Environment Agency, available at www.arso.gov.si. Six meteorological factors were assessed for the central Slovenian region (capital city Ljubljana), including average daily air temperature at two meters above ground (°C), average daily relative humidity (%), average daily solar radiation (hours), average daily wind speed (m/s), average daily cloud cover (sky cover in %) and average daily air pressure (hPa).

Ethics Statement

The Ethics Committee of the University Medical Center Ljubljana waived the need for ethical approval and the need to obtain consent for the collection, analysis, and publication of the retrospectively obtained and anonymized data for this non-interventional study (Document number 000019c6-000032a4).

Statistical Analyses

The data were analysed using the R statistical software, version 4.0.3, with the additional packages from the tidy verse ecosystem. The demographic, clinical and epidemiological characteristics of the newborns were presented as frequencies, means and standard deviations. Numerical variables were analysed using the two-sample independent t test or Mann-Whitney U test. Categorical variables were analysed using the Fisher's exact test. The meteorological data were presented graphically as mean values. The correlations and multiple regression were calculated, where the number of virus positive cases was the dependent variable, and the meteorological factors were the independent variables. The absence/presence of VRTI in relation to the meteorological factors was calculated with the ROC curve, where the cut-off value was calculated as the Youden index. The P value <0.05 was considered statistically significant.

Results

The demographic, clinical and epidemiological characteristics of the study population and the differences between newborns with RSV and non-RSV viral respiratory tract infection is presented in Table 1.

A typical seasonal distribution of newborns with VRTI was observed, as 86.4% of them were admitted to the hospital from December to March. The overall VRTI incidence reached peak at week 7, accounting for 10.5% of all annual VRTI cases. This peak was reached almost entirely due to RSV VRTI

Table 1. Demographic, Clinical and Epidemiological Characteristics of Study Population and Differences between Newborns with Respiratory Syncytial Virus (RSV) and non-RSV Viral Respiratory Tract Infection*

Characteristics	Study population N=228	RSV† infection N=181	Non-RSV† infection N=47	P value‡
Gender				
Male	128 (56.1)	100 (55.2)	28 (59.6)	0.624
Female	100 (43.9)	81 (44.8)	19 (40.4)	
Gestational age (weeks)	37.1±3.6	37.9±2.8	34.8±4.6	<0.001
Preterm	67 (29.5)	39 (21.5)	28 (59.6)	<0.001
Birth weight (grams)	3052±900	3219±761	2620±1050	<0.001
Breastfed	160 (70.7)	141 (77.9)	19 (40.4)	<0.001
Palivizumab	11 (4.8)	4 (2.2)	7 (14.9)	0.002
Risk factors for infection				
Positive epidemiological history	172 (75.4)	143 (79.0)	29 (61.7)	0.026
Siblings	168 (73.4)	132 (72.9)	36 (76.6)	0.368
Risk factors for severe disease				
Bronchopulmonary dysplasia	10 (4.4)	5 (2.8)	5 (10.6)	0.034
Congenital heart disease	9 (3.9)	6 (3.3)	3 (6.4)	0.186
Age (postmenstrual) at infection onset (days)	23.8±20.3	21.1±15.8	34.5±30.1	<0.001
Age (postmenstrual) at admission (days)	26.4±20.3	23.6±15.7	37.7±30.4	<0.001
Aetiology				
RSV	181 (79.4)	181 (100.0)	0	<0.001
Human rhinovirus	28 (12.2)	0	28 (59.6)	<0.001
Human metapneumovirus	6 (2.6)	0	6 (12.8)	<0.001
Parainfluenza virus	6 (2.6)	0	6 (12.8)	<0.001
Influenza virus	5 (2.2)	0	5 (10.6)	<0.001
Human bocavirus	4 (1.8)	0	4 (8.5)	<0.001
Human coronavirus	3 (1.3)	0	3 (6.4)	<0.001
Complications				
Apnea	93 (40.7)	67 (37.0)	26 (55.3)	0.030
Atelectasis	74 (32.5)	62 (34.3)	12 (25.5)	0.296
Bacterial superinfection	102 (44.7)	81 (44.8)	21 (44.7)	1.000
Sepsis	14 (6.1)	10 (5.5)	4 (8.5)	0.496
Length of hospitalization (days)	9.2±7.0	8.9±5.4	10.5±11.2	0.144
Length of NICU§ hospitalization (days)	3.3±4.8	3.1±4.7	3.9±5.1	0.343
Treatment				
Oxygen	199 (87.3)	159 (87.8)	40 (85.1)	0.626
Non-invasive ventilation	100 (43.9)	80 (44.2)	20 (42.6)	0.870
Invasive ventilation	74 (32.5)	56 (30.9)	18 (38.3)	0.383
Length of treatment (days)				
Oxygen	4.5±5.2	4.4±4.7	4.8±6.8	0.658
Non-invasive ventilation	1.4±2.2	1.4±2.1	1.2±2.4	0.679
Invasive ventilation	2.4±4.0	2.2±4.0	2.9±4.2	0.306

*Categorical and continuous variables presented as frequency (percentage) and mean±SD, respectively; †Respiratory syncytial virus; ‡Fisher's exact test or two-sample independent t test; §Neonatal intensive care unit.

(91.7%), which also peaked during the same week, while the incidence of non-RSV VRTI peaked at week 12. There was a correlation between the air temperature and the occurrence of VRTI (r=-0.40, P<0.001). The multiple linear regression model showed a strong relation between these two parameters (r^2=0.2326, P=0.01). The air temperature during the VRTI season was significantly lower than in the off-season (5.9 vs. 12.7 °C, P<0.001) and the occurrence of VRTI started to rise below the air temperature of 10.6 °C (sensitivity 0.83, specificity 0.60).

The correlation between the air temperature and the occurrence of RSV VRTI was also clear (r=-0.37, P<0.001). The air temperature during the RSV season was notably lower than in the off-season (4.9 vs. 12.7 °C, P<0.001) and the occurrence of RSV infections started at temperatures below 10.9 °C (sensitivity 0.89, specificity 0.58). The air temperature also correlated with the occurrence of non-RSV VRTI (r =-0.21, P<0.001). The temperature was lower during the non-RSV season than in the off-season (8.3 vs. 12.7 °C, P<0.001) and the occurrence of non-RSV VRTI started below the temperature of 10.5 °C (sensitivity 0.71, specificity 0.60). The comparison of air temperature when RSV and non-RSV VRTI occurred showed a difference of 3.4 °C; RSV VRTI started at 4.9 °C and non-RSV VRTI at 8.3 °C (P=0.001). At below 3.8 °C, RSV VRTI were more probable than non-RSV VRTI (sensitivity 0.75, specificity 0.47).

There was a correlation between the relative humidity and the occurrence of RSV VRTI (r=0.096, P<0.05). However, no correlation was found between the relative humidity and the occurrence of VRTI (r=0.082, P>0.05) and non-RSV VRTI (r=0.0028, P>0.05). Higher relative humidity was observed during the VRTI and RSV VRTI season compared to the off-season (76.9 vs. 74.7%, P=0.028; 77.4 vs. 74.7%, P=0.016, respectively). VRTI and RSV VRTI were more probable when the relative humidity was above 76.5% (sensitivity 0.56, specificity 0.55; sensitivity 0.58, specificity 0.55; respectively). No difference in relative humidity was found between the occurrence of RSV and non-RSV VRTI.

The daily solar radiation correlated with the occurrence of VRTI (r=-0.24, P<0.001) and RSV VRTI (r=-0.25, P<0.001), however it did not correlate with the occurrence of non-RSV VRTI (r=-0.071, P>0.05). The daily solar radiation was shorter during the VRTI and RSV VRTI season compared to the off-season (4.0 vs 5.6 hours, P<0.001; 3.5 vs. 5.6 hours, P<0.001, respectively) and a difference of more than two hours was noticed during the RSV VRTI season. A significant difference in daily solar radiation was also observed when comparing the occurrence of RSV and non-RSV VRTI (3.5 vs. 5.0 hours, P=0.017); with daily solar radiation below 7.1 hours, the occurrence of RSV VRTI was more probable than non-RSV VRTI (sensitivity 0.42, specificity 0.78).

The cloud cover correlated with the occurrence of VRTI (r=0.11, P<0.05) and RSV VRTI (r=0.14, P<0.05), but not non-RSV VRTI (r=-0.018, P>0.05). However, increased cloud cover was only observed during the RSV VRTI season compared to the off-season (67.8 vs 61.6%, P=0.017). No difference in the cloud cover was found between the occurrence of RSV and non-RSV VRTI.

There was no correlation between wind speed and the occurrence of VRTI, RSV and non-RSV VRTI. Moreover, no difference in wind speed was found between the occurrence of VRTI, RSV VRTI and non-RSV VRTI compared to the off-season. No correlation between air pressure and the occurrence of VRTI, RSV and non-RSV VRTI was found. The air pressure also did not differ during the VRTI, RSV VRTI and non-RSV VRTI season compared to the off-season. The only difference in air pressure was observed when comparing the occurrence of RSV VRTI and non-RSV VRTI; the air pressure was lower during the RSV season compared to the non-RSV season (981.6 vs. 984.6 kPa, P=0.033). The weekly occurrence of RSV and non-RSV VRTI from January 2015 to December 2020 and their relation to air temperature, daily solar radiation, relative humidity and cloud cover is presented in Fig. 1.

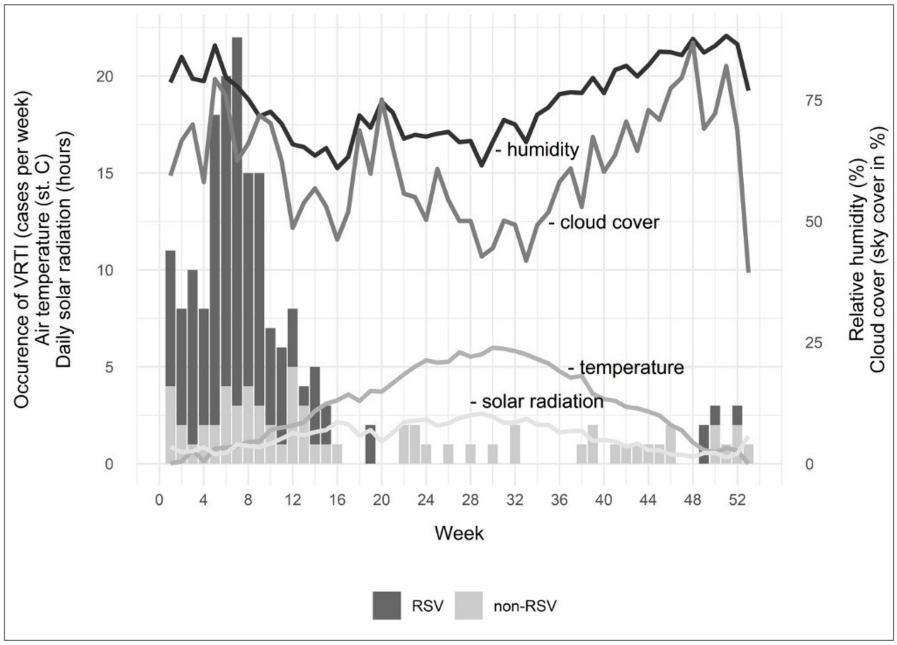

Fig. 1. *Weekly Occurrence of Respiratory Syncytial Virus (RSV) and non-RSV Viral Respiratory Tract Infections (VRTI) from January 2015 to December 2020 and their Relation to Air Temperature, Daily Solar Radiation, Relative Humidity and Cloud Cover.*

Discussion

This study demonstrates the significant relation of meteorological factors to neonatal VRTI occurrence. Low air temperature, high relative humidity, shorter daily solar radiation and increased cloud cover were associated with increased risk of VRTI, RSV VRTI or non-RSV VRTI. Similar studies in temperate climates found comparable conclusions for adult and paediatric patients (11–15), however, to the best of our knowledge, this is the first study of this kind on neonatal patients. The study shows an evident correlation and strong relation between the air temperature and the occurrence of VRTI, RSV VRTI and non-RSV VRTI. From our data, we can anticipate the occurrence of neonatal VRTI at average daily air temperatures below 4.9 °C. Furthermore, if the air temperature drops below 3.8 °C, neonatal RSV VRTI occur more frequently than non-RSV VRTI. These two specific values could predict the onset of the VRTI and RSV VRTI season. To investigate this assertion, we compared our meteorological model with established epidemiological methods for defining RSV seasonality, involving the onset, offset, peak and duration of the RSV epidemic season. Until recently, two consecutive weeks with more than 10% of samples testing positive for RSV defined the onset of the RSV epidemic season in Slovenia. However, due to delayed determination of season onset, Grilc et al tested other possible methods to find the most appropriate one for defining RSV seasonality (9). They evaluated ten consecutive RSV seasons from 2008 to 2018 in Slovenia by using four different calculation methods. The first was the ≥10% method already implemented (16), including its modifications, using the ≥3, ≥5 and ≥7% rule (17). These methods enable real time RSV season evaluation. The second method, used by the European Centre for Disease Prevention and Control, retrospectively defines season weeks when weekly RSV detections exceed 1.2% of the total RSV-positive specimens per season (18). The third, also a retrospective method used in the United Kingdom, defines RSV season weeks when the average weekly number of RSV-positive specimens accounts for ≥60% of each year's average (19). The fourth method evaluated was the moving epidemic method, which prospectively monitors the weekly intensity level of RSV VRTI (20). The authors concluded that calculation methods are still the most conclusive; the ≥3% calculation method could be used to define the beginning of the RSV season, and the ≥7% calculation method to define the epidemiological parameters of an ongoing season and to support the public health response.

Furthermore, we combined our meteorological data on air temperature and their epidemiological data on RSV seasonality. The air temperature seemed to be a good predictive factor of the onset of the RSV season, as the difference using the ≥3% calculation method ranged from one to seven weeks, on average three weeks. In most cases the air temperature preceded the calculation method, thus offering a probably even more prompt, real-time predictive method for daily clinical practice.

The peak RSV season is defined as the week with the highest percentage of positive patients. The difference in the peak RSV season, estimated using the lowest average air temperature and the 7% calculation method, ranged from one to 10 weeks, on average five weeks. The calculated peak RSV week occurred in the middle third of the RSV season, although this was less obvious in the case of the lowest average air temperature, which also occurred during the first or last third of the RSV season. Overall, the lowest average air temperature did not predict the peak RSV season very well.

The difference in the offset RSV season, estimated by the average air temperature and the 7% calculation method, ranged from seven to 10 weeks, on average seven weeks. This extended interval seemed too long to provide any reasonable accuracy in relation to air temperature to predict the offset and consequently the duration of the RSV season.

The difference in RSV season duration, estimated by the average air temperature and the 10% calculation method (due to missing data for the 7% calculation method during the 2018/2019 season), ranged from zero to five weeks, on average 0.5 weeks. This slight difference appeared insignificant and the average air temperature could be interpreted as a good predictor of RSV season duration, but due to this difference in the onset and offset of the season, this assertion appeared less convincing.

The earth's ground and air temperatures are fundamentally related to solar radiation. Shorter daily solar radiation during the winter therefore decreases the air temperature, and the effectiveness of solar radiation is additionally decreased by clouds. With this perspective, the association of daily solar radiation, cloud cover and the occurrence of VRTI in our study appeared convincing and consistent with the findings of other, similar studies (21).

Besides air temperature, the occurrence of VRTI and especially RSV VRTI was also related to relative humidity. High relative humidity was associated with increased risk of VRTI and RSV VRTI, which was also observed in other studies in temperate climates (12,14,15,21). Respiratory viruses are spread by water droplets, and at low air temperatures their viability probably increases as relative humidity increases. Some similar studies report increased RSV VRTI probability at low absolute humidity (11,22). Absolute humidity represents the density of water vapor, and relative humidity is the ratio between absolute humidity and saturated humidity (the maximum possible absolute humidity) at a given temperature. This means that low absolute humidity at a lower temperature increases relative humidity, which is usually observed during winter months in temperate climates, and likewise consistent with our and their findings.

Due to the high burden of neonatal VRTI, especially due to RSV, several preventive strategies are used, focusing mainly on maternal and infant immunization (8). Currently, two humanized monoclonal antibodies (palivizumab and nirsevimab) are licensed for RSV prevention. Immunoprophylaxis with these drugs should preferably start before the onset of the RSV season. According to Slovenia's multi-year RSV seasonality, the recommended time to start immunoprophylaxis is week 48. Comparing this with our data showing that the air temperature falls below 3.8 °C during weeks 47–50, this might lead to the firm conclusion that air temperature drop below 3.8 °C could be used as an early warning sign of RSV season onset and the need for immunoprophylaxis.

Limitations of the Study

Some limitations of this study are worth noting. The prognostic accuracy of the meteorological data analysed in this study is limited to the central part of Slovenia with a continental climate, and does not relate to all the Slovenian regions, which are influenced by sub-mediterranean and alpine climates. Although Slovenia is one of the smallest European countries, and as there is a strong interaction between these three climatic systems across most of the country, specific regional meteorological analysis would be necessary to predict its influence on neonatal VRTI occurrence accurately.

Another interfering factor might be the air pollution, which affects the infant lung health, especially after chronic exposure (23). As the granted access from the Slovenian Environment Agency covered only the set of meteorological data, in which the air pollution was not comprised, this study did not evaluate the possible synergistic effect of meteorological factors and air pollution on VRTI occurrence. Further studies should assess this possibility. Furthermore, VRTI are seasonal diseases, but they are not solely related to meteorological factors. This was most obviously seen during the very atypical 2021/2022 season, when RSV VRTI already started during the summer in week 27. This extremely early occurrence was most probably related to the termination of the previously strict prevention measures against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. VRTI are therefore multifactorial diseases, influenced by meteorological, microbiological, immunological, epidemiological, environmental and other factors as well. Using only meteorological factors for prediction of the VRTI season might be completely inadequate and incorrect if other factors are trending unusually or differently. Finally, meteorological conditions also affect human social behaviour, as we rather stay indoors during cold and humid winter months. This leads to more frequent and closer social contacts which are inherently crucial for effective viral spread.

Conclusion

Meteorological factors, particularly air temperature and relative humidity, were associated with neonatal VRTI occurrence in the temperate climate of central Slovenia. The average daily air temperature below 4.9 and 3.8 °C could predict the onset of the VRTI and RSV VRTI season, respectively. These factors could be used as real-time predictive warning, especially for RSV season onset and the need to begin RSV immunoprophylaxis in vulnerable newborns. To adjust preventive strategies in general, and to reduce the incidence and burden of these seasonal infections, adverse meteorological conditions in different geographical areas should be studied, also comprising other possible modifying factors like air pollution.

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Conflict of Interest: The author declares that he has no conflict of interest.

Data Statement: The data that support the findings of this study are available from the corresponding author upon request.

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