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ORIGINAL RESEARCH

Epidemiology of respiratory syncytial virus in children ≤2 years of age hospitalized with lower respiratory tract infections in the Russian Federation: a prospective, multicenter study

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Background: Respiratory syncytial virus (RSV) is the leading cause of severe lower respiratory tract infections among infants and young children, and is responsible for an estimated four million deaths per year globally. A monthly injection of palivizumab has been used for prophylaxis of serious RSV infections among high-risk children in 71 countries since 1998 and approval for use in the Russian Federation was obtained in February 2010. A recommendation for RSV prophylaxis in the Russian Federation would require knowledge of the prevalence and seasonality of RSV in that country.

Methods: In a prospective, multicenter, epidemiological study of the prevalence, seasonality, and peak occurrence of RSV infection, children aged ≤2 years hospitalized for lower respiratory tract infections in three regions of the Russian Federation, from September 2008 through April 2009, were screened and tested for RSV using rapid immunochromatography of nasopharyngeal lavage. For subjects who were tested positive, hospitalization data were collected.

Results: Of 519 children aged ≤2 years enrolled from September 11, 2008 through April 26, 2009, 197 tested positive for RSV (38.0%, 95% CI: 33.8, 42.3). The onset of the 2008–2009 RSV season in the Russian Federation occurred in late October 2008, similar to what is observed in other northern temperate zones. Peak activity occurred in early April 2009, when 62% of children enrolled tested positive for RSV.

Conclusion: The prevalence of serious RSV infections in the Russian Federation is similar to the prevalence previously identified in other temperate zones of the northern hemisphere. The seasonality of disease shifted towards early spring, with peak activity later in the season, within a range reported in other countries. These data provide further evidence of serious RSV infection in children in the Russian Federation, as well as guidance for timing of seasonal RSV prophylaxis, especially among individuals at high risk for serious RSV infection.

Keywords: RSV, prophylaxis, prevalence, seasonality, palivizumab

Introduction

Respiratory syncytial virus (RSV) is currently considered the single most important cause of childhood respiratory infection.[1,2] The World Health Organization reports four million deaths annually worldwide among children aged <5 years due to the virus.[3] The primary cause of severe lower respiratory tract infection (LRTI) globally among infants aged <2 years, the virus is the leading cause of hospitalizations for a LRTI during respiratory virus season. Premature infants with underdeveloped lungs and an immature immune system are particularly vulnerable to serious infections from RSV.[1,2,4–6] The transmission of RSV is difficult to prevent because it is easily

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transmitted by unprotected coughing or sneezing, or contact with contaminated hands.[7] As many as 60% of all children are infected with RSV in their first year of life and almost 100% within their second year of life.[8] RSV does not stimulate a robust immunological response, therefore reinfection is common.[9]

Unfortunately, once children are infected with the virus, there are no etiopathogenetic treatment options available. Routine use of bronchodilators, epinephrine, steroids, and ribavirin has proven to be of no significant benefit; therefore, treatment has been limited to supportive measures.[10]

Palivizumab (Synagis®; MedImmune Inc, Gaithersburg, MD; marketed outside the USA by Abbott Laboratories, Abbott Park, IL) is a humanized IgG1 monoclonal antibody targeting the F protein of RSV. When administered monthly while RSV is circulating in the community, palivizumab has been shown to reduce severe RSV disease requiring hospitalization in high-risk children (ie, those born ≤35 weeks gestational age; those with bronchopulmonary dysplasia; and infants with hemodynamically significant congenital heart disease who were less than two years of age at the start of RSV season), by approximately 50% compared to placebo.[11,12] Approved in the United States in 1998, palivizumab received European approval in 1999, and its approval in the Russian Federation was received in February 2010. Optimal timing of prophylaxis is based on epidemiological data.

A review of literature published over a 30-year period regarding RSV seasonality and epidemiology disclosed that RSV season in the northern hemisphere roughly starts in September and ends in April.[5,6] European countries, including those countries near Russia, with published data, had similar RSV seasons that started as early as September, and ended as late as July.[13–24] In the Nordic countries of Finland, Denmark, Norway, and Sweden, RSV season begins in October or November and continues through March or April, with peak activity in December/January.[5,18,25] In Norway, RSV has been reported through June, with later peak activity in January/February.[14] Although the Russian Federation covers a very large territory, including arctic areas and subtropics, most of its population occupies temperate regions.

The objective of this study was to describe the prevalence and seasonality of RSV infection in children aged ≤2 years, hospitalized for LRTI between September 2008 and April 2009, in three temperate regions of the Russian Federation. Demographic information, morbidity, and risk factors are also reported.

Methods

This prospective, multicenter, observational study was conducted at nine participating hospital centers located in three regions: seven in Moscow (Central), one in Saint Petersburg (Northwest), and one in Tomsk (East). The study included parental written informed consent and received approval from the Institutional Ethics Boards of all participating centers. The timing of the study, from September 2008 through April 2009, allowed essential epidemiological information on RSV to be obtained during the cold season in the northern hemisphere when RSV is most prevalent. The plan was to enroll approximately 500 eligible children into the study over the period.

Study population

All children with LRTI hospitalized at participating centers were potentially eligible for enrollment. The determination of LRTI was based on a medical diagnosis of acute bronchiolitis, bronchitis, and/or pneumonia, and based on the presence of symptoms (cough, coryza, rhinorrhea, fever, or retractions) and signs (wheezing, crackles, or rales). Children with at least one symptom and a chest radiograph diagnostic of bronchiolitis, pneumonia, or bronchitis were also designated as having an LRTI. Additionally, apneic events with accompanying auscultatory findings, chest radiograph of LRTI, clinical symptoms of fever, or coryza were designated an LRTI episode.

Eligibility requirements also included age ≤2 years at the time of hospital admission and hospitalization <24 hours prior to RSV testing. Enrollment was prohibited if the child had received any product containing RSV-neutralizing antibodies (including hyperimmunoglobulins) within 100 days of enrollment, or had participated in a clinical trial for RSV treatment or prophylaxis prior to or during the hospitalization.

Procedures

Physical examination was performed and a parent provided information regarding the child's personal and family medical and social history during a single screening and enrollment visit prior to RSV testing. The RSV diagnostic test method utilized was approved for use by regulatory authorities in the Russian Federation. Nasopharyngeal lavage was collected and evaluated within 24 hours of hospitalization, using a rapid immunochromatographic RSV detection technique, QuickStripe™ RSV (Savyon Diagnositics Ltd, Ashdod, Israel). Two retests could be conducted within 24 hours of enrollment if the initial test results were inconclusive.

A classification of children at "high-risk" for serious RSV infection was made based on a medical history of premature birth (≤35 weeks of gestational age); chronic lung disease (CLD), including bronchopulmonary dysplasia (BPD); or congenital heart disease (CHD). The details of hospital stay and discharge were recorded from the hospital medical records using study-specific case report forms only for RSV-positive (RSV+) children. No hospitalization data were recorded for RSV-negative (RSV–) children. No subsequent visits were required for any enrolled child and no interventions were assessed in the study.

Data analysis

All children enrolled in the study formed the analysis population for primary and secondary analyses, irrespective of RSV diagnosis. The primary analysis, RSV prevalence, was determined by the number and proportion of RSV+ children (95% exact confidence interval [CI] for the proportion), calculated by dividing the total number of RSV+ children by the total number of children tested for RSV.

Seasonality was determined within the study period of September 2008 through April 2009. The number and proportion of RSV+ children enrolled was calculated at weekly intervals and across the entire study period. Calculations were performed for the total enrollment overall and for children from each of the three individual geographic areas.

Characteristics were evaluated using descriptive statistics. Means and standard deviations were calculated for continuous variables. For categorical variables, the number and percentage of enrollees in each category within an assessment were calculated.

Length of hospital stay, use and duration of oxygen supplementation, use of mechanical ventilation, use and duration of continuous positive airway pressure (CPAP), admission to an intensive care unit (ICU), duration of stay at ICU, and mortality were summarized descriptively. For continuous variables, comparisons of RSV+ children that were at "high risk" and "not at high risk" for serious RSV infection (based on medical history as described in Methods) were made using a one-way analysis of variance (ANOVA) with group as the only factor. For categorical variables, the number and percentage of children in each category within an assessment were calculated for non-missing data, and comparisons of RSV+ children that were at "high risk" and "not at high risk" for serious RSV infection were made using Fisher's exact test. *P*-values were based on two-tailed tests. Tests resulting in a *P value* ≤ 0.05 were considered statistically significant.

Risk and protective factors were descriptively compared between RSV+ and RSV– children. No statistical tests were performed on these comparisons.

Results

Enrollment

Screening and enrollment began on September 11, 2008 with four active centers. The number of centers increased gradually to nine by February 2009, and continued through to the end of enrollment on April 26, 2009. Three centers (two in Moscow and one in Tomsk) had two enrolling locations each.

Of 593 children aged ≤2 years assessed for inclusion in the study, 520 were enrolled. The primary reason for non inclusion was parental unwillingness to provide consent. The withdrawal of consent occurred for one enrolled child prior to RSV testing. The total data set for this study comprised the remaining 519 children.

Table 1 summarizes the demographic characteristics of all children enrolled, of the RSV+ subset, and of high-risk RSV+ individuals by location. Children with RSV+ were predominantly full-term, white, males, of an appropriate weight for gestational age, and 7.5 months of age, on average, at hospitalization. These characteristics were similar to those of the total set; however, the mean age at hospitalization in the RSV– subset was 9.7 months.

In physical examination conducted at enrollment, vital signs (mean ± SD) were similar among the subsets: respiratory rate (40.9 ± 10.60 breaths·min^{-1}) and heart rate (130.5 ± 12.88 b·min^{-1}), oxygen saturation (96.0 ± 2.60%), temperature (37.0 ± 0.58°C), length (68.9 ± 10.09 cm) and body weight (8.5 ± 2.69 kg).

Prevalence and seasonality of RSV

During the period of September 11, 2008 through April 26, 2009, 197 of 519 children enrolled were RSV+ (38.0%, 95% CI: 33.8–42.3). The prevalence of RSV was highest in Moscow, where 151 of 362 children enrolled were RSV+ (41.7%, 95% CI: 36.6–47.0). In St. Petersburg, RSV was identified in 19 of 50 children enrolled (38.0%, 95% CI: 24.7–52.8), and 27 of 107 children enrolled were RSV+ (25.2%, 95% CI: 17.3–34.6) in Tomsk.

The onset of RSV occurred in Moscow during week 44 (late October) of 2008 (Figure 1). Peak RSV activity occurred during week 14 of 2009 (early April), when 62% of children with LRTI enrolled were RSV+ (31/50, 95% CI: 47.2–75.4). During the following two weeks, at the end of the recruitment phase, the proportion of RSV+ children among those

Table 1 Demographic characteristics at enrollment

	All (N = 519)	RSV+ (N = 197)	High-risk RSV+[a]	
			Moscow (N = 17)	St. Petersburg (N = 1)
Males (%)	330 (64)	120 (61)	10 (59)	1 (100)
White race (%)	505 (97)	195 (99)[b]	17 (100)	1 (100)
Age (months; mean ± SD)	8.8 ± 6.37	7.5 ± 5.86	8.6 ± 7.1	11.0 ± 0.0
Birth weight (kg; mean ± SD)	3.3 ± 0.61	3.4 ± 0.66	2.2 ± 0.7	2.1 ± 0.0
Gestational age (weeks; mean ± SD)	39.0 ± 2.2	38.9 ± 2.4	33.6 ± 3.7	32.0 ± 0.0
Multiple birth (%)	25 (5)	13 (7)	5 (29)	0 (0)

Notes: [a]No high-risk RSV+ children were enrolled in Tomsk. [b]Two children were Asian. High-risk was defined as a medical history of at least one of the following conditions: premature birth (≤35 weeks of gestational age); chronic lung disease/bronchopulmonary dysplasia; or congenital heart disease. RSV+ diagnosis made by immunochromatographic testing of nasopharyngeal lavage.
Abbreviations: RSV+, respiratory syncytial virus positive; SD, standard deviation.

enrolled decreased to 39% (11/28, 95% CI: 21.5–59.4). The protocol-defined duration of the study did not allow for a determination of season offset.

Morbidity and mortality

Among high-risk RSV+ children, the length of hospital stay ranged from 4–13 days vs 1–37 days among RSV+ children without high-risk conditions. More of the RSV+ children at high risk for serious RSV infection required oxygen supplementation than the other RSV+ children not at high risk (28% v 10%, $P = 0.04$). The maximum duration of oxygen supplementation was 7–10 days, irrespective of risk category. No mechanical ventilation, CPAP, or surgeries were required and there were no deaths.

Risk and protective factors

Physiological risk factors have been described above. In addition to those already presented, family and social history factors were identified and are described in Table 2. In the RSV+ subset at high risk for serious RSV infection, 14 children were born premature, two had a history of CHD, and two had a history of CLD/BPD. Two criteria were identified for one high-risk child with RSV+ who was born premature and had a history of BPD. Medical histories revealed one or more hospitalizations in the high-risk RSV+ subset (50%), compared with the RSV+ (25%) and RSV− (37%) subsets not at high risk. Similarly, in the high-risk RSV+ subset, 50% of the children had been admitted to an ICU at birth, compared with 4% in the RSV+ and 7% in the RSV− subsets not at high risk.

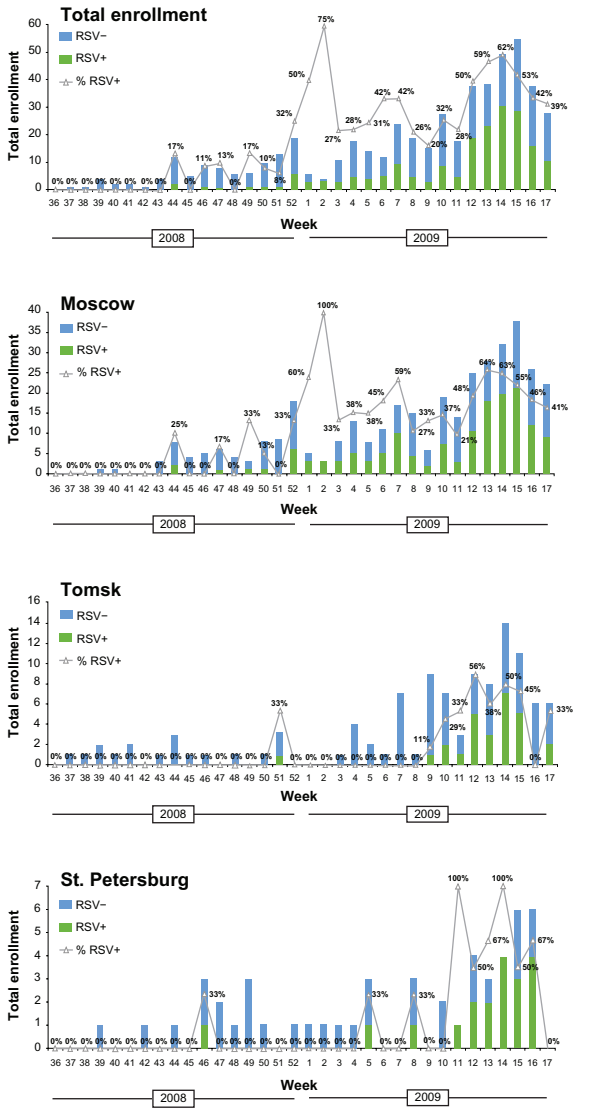

Figure 1 Rates of enrollment over the study period at weekly intervals and RSV prevalence overall and by city. The onset of the RSV season occurred in late October 2008 (week 44), and peak activity was observed between weeks 10 and 17 of 2009 (March–April). In all locations, RSV+ enrollments increased dramatically in weeks 12 to 15 of 2009 (March–April), near the end of the period studied.

Discussion

The prevalence of RSV during the 2008–2009 season in the Russian Federation was consistent with that expected in a northern temperate zone. The peak of RSV activity occurred in March–April. Both the prevalence of RSV and the peak of RSV activity were similar in the three participating cities. An abnormally warm autumn and a late winter cold-weather onset were recorded in temperate regions of the Russian Federation during the 2008–2009 season.[26] This unexpected factor serves as a reminder that a single season may not be representative of the RSV season from year to year.

Table 2 Prevalence of risk factors among RSV+ and RSV– children

	RSV+ (N = 197)	RSV– (N = 322)
Mother smoked tobacco during pregnancy (%)	28 (14)	66 (21)
Passive cigarette smoke exposure in home (%)	90 (46)	186 (58)
Number of siblings in the home (mean ± SD)	0.8 ± 0.75	0.7 ± 0.70
Age of youngest sibling in the home (years; mean ± SD)	4.0 ± 2.62	4.4 ± 2.84
Number of people living in the home (mean ± SD)	3.4 ± 1.19	3.5 ± 1.42
Daycare attendance (%)	4 (2)	12 (4)
Number of furred pets inside home (mean ± SD)	0.4 ± 0.68	0.5 ± 0.73
Family history of atopy (%)	38 (19)	69 (21)
Months breastfed (mean ± SD)	4.6 ± 4.68	4.9 ± 4.50

Note: RSV+/RSV– diagnosis made by immunochromatographic testing of nasopharyngeal lavage.
Abbreviations: RSV+, respiratory syncytial virus positive; RSV–, respiratory syncytial virus negative; SD, standard deviation.

Considering the variability reported in published epidemiological studies, the late arrival of the RSV peak was not exceptional. Russia may have an epidemiology similar to that of Finland, Sweden, and Norway, where later seasons are a regular occurrence not associated with the weather, and RSV peaks in March–April.[18] Such variability is not only found in far north or northeastern European countries. In Croatia, RSV seasons have two-year cycles, with seasons occurring from October to April one year and from December to June the next year, and with corresponding peaks in December–January and March–May.[13,21] In Ireland, RSV onset occurs in November and year-to-year, the RSV peaks vary in occurrence from December through February.[27] The RSV peak reported in Germany appears to be dependent upon the timing of RSV season onset, such that when onset is in December, peak activity has been reported in March.[22,23] In Italy, RSV onset occurs in December, peaks in March, and offsets in April.[28,29] In Turkey, RSV peaks in March, with onset in September and offset in May.[24]

The prospective design of this study contributed to the generalizability of results. All children with LRTI hospitalized in the participating centers were regarded as potential candidates for the study; therefore, the study was designed to represent the general population and to evaluate the prevalence of risk factors for RSV+ LRTI. By design, demographic data, risk and protective factors, and other descriptive information of the study population were collected without bias before the RSV test was administered.

Demographic characteristics and risk factors for severe RSV infection identified in the Russian Federation were consistent with those in other developed countries where children most at risk are those born premature, with chronic lung disease, or with congenital heart disease.[19,30] Risk factors for hospitalization, such as sex (male); low birth weight (<10th percentile); exposure to school-age children in the home; daycare attendance; failure to breast feed beyond two months; cigarette smoke exposure; crowded living conditions; chronologic age <six months at the time of RSV exposure; and being underweight at birth,[31,32] were also factors in the children with RSV+ LRTI. It is important to keep in mind that in previous studies, children born shortly before or during the RSV season were significantly more likely to be hospitalized for RSV+ LRTI than children born during other periods of the year.[31,32] These implications are key in that children who are at the highest risk of infection and complications leading to hospitalization are those most in need of prophylaxis.

Limitations of the study that may have influenced the results include the sensitivity of the rapid immunochromatographic RSV detection method (70%–90%), leaving a potential 10%–30% margin of error in identifying RSV infections. Enrollments in St Petersburg and Tomsk were relatively low and each city had only one participating site, therefore the prevalence of RSV in those cities may not have been adequately captured. Additional studies would be needed to provide a more precise definition of the RSV season than those provided by data collected during a single season. Although it can be argued that such factors can be generalizable for all regions of the Russian Federation as a whole, the epidemiological data collected in this study remain both valuable and important as they are consistent with what has been documented globally and in Europe concerning RSV.

This study confirms that RSV is widespread among populations in three major temperate regions of the Russian Federation and is a significant cause of LRTI leading to the hospitalization of young children. During one RSV "season", September 2008 through April 2009, enough data were obtained to evaluate the burden and need for RSV prophylaxis in high-risk infants. Inclusion criteria ensured homogeneity of the population and objective, evidence-based medical diagnosis procedures were adequate to support a conclusion regarding the disease prevalence and seasonality. All of these factors contribute to the generalizability of the results for the purposes intended; specifically, the preparation of health facilities to meet the burden of care and the effective timing of RSV prophylaxis with palivizumab.

Conclusion

RSV was a major contributor to LRTI hospitalization in the Russian Federation from October 2008 through April 2009.

Its prevalence among hospitalized children ≤two years of age was consistent with that in other developed countries. The 2008–2009 RSV season in the Russian Federation had an onset similar to other northern temperate zones. Although the period of peak activity occurred in March–April, later than previously reported in temperate regions of the northern hemisphere (December–January), it was not exceptional or inconsistent with ranges reported overall. The seasonality of RSV was similar with respect to onset and peak RSV activity between each of the three participating cities (regions). The demographics and risk factors identified among children hospitalized with RSV were similar to those described outside of the Russian Federation. These data support the consideration of an effective time period for RSV control measures, including RSV prophylaxis in children at high risk for serious RSV infection requiring hospitalization.

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KG, AC, GS, RP, and GN are employed by Abbott Laboratories. AC, GS, RP, and GN hold stocks in Abbott Laboratories. VT, VU, and AG have served as consultants to Abbott Laboratories.

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