

Respiratory syncytial virus infection in a selected sample of infants hospitalized for lower respiratory tract infection in Lithuania and Estonia

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Background. The study presents data on a sample of children under one year of age hospitalized with lower respiratory tract infections (LRTIs) in Lithuania and Estonia.

Subjects and methods. This large, retrospective, cross-sectional, observational epidemiologic survey was conducted in 12 countries in Central and Eastern Europe. Eligible subjects were under one year of age, hospitalized for LRTIs, for whom RDT (Rapid Diagnostic Test) was performed. Physicians completed questionnaires at discharge or on the first check-up visit after hospitalization. To test for RSV, the immunochromatographic method was used in Lithuania, and immunofluorescence or the PCR methods were applied in Estonia.

Results. In two countries, 482 patients fulfilling the definition of a LRTI case (i.e., children below one year of age hospitalized with a diagnosis of bronchiolitis and/or pneumonia) were enrolled during two consecutive RSV seasons. Bronchiolitis was the most common diagnosis (84%). In Lithuania and Estonia, 36.6% and 83.3% of cases were conscious at admission. RSV was confirmed in 87.3% and 54.2% of tested LRTI cases in Estonia and Lithuania, respectively. Intensive care unit hospitalization was required for 9.1% of LRTI cases in Lithuania and for 3.1% of cases in Estonia. Supplemental oxygen was required for 23.2% and 31.6% in cases in Lithuania and Estonia, respectively. In Lithuania, complete recovery at discharge was assessed for 35.8% of LRTI cases and improvement in 62.2% of cases. In Estonia, all LRTI cases were improved at discharge and there were no complete recoveries.

Conclusion. RSV was prevalent among children hospitalized for LRTI in Lithuania and Estonia; bronchiolitis was the most common diagnosis in hospitalized patients.

Keywords: lower respiratory tract infections, respiratory syncytial virus, hospitalization

INTRODUCTION

Lower respiratory tract infections (LRTIs) are a major cause of morbidity in infants and children worldwide. The respiratory syncytial virus (RSV), influenza, the human parainfluenza virus (1), and the human metapneumovirus (2) are several of the viruses responsible for LRTI hospitalization in infants. RSV, an enveloped single-stranded RNA virus of the *Paramyxoviridae* virus family, is the most common cause of LRTI in children below one year of age (3).

The respiratory syncytial virus is transmitted by aerosolized droplets or by direct contact with secretions or contaminated surfaces (3). The incubation period for RSV is 2–8 days on average (3). Initial symptoms of infection include congestion and coryza (rhinitis), often accompanied by a low-grade fever; at this point, RSV is usually confined to the nasopharynx. However, 2–5 days after the onset of symptoms, the infection may spread to the lower respiratory tract (4).

Virtually all individuals experience RSV infection within the first two years of life, usually within the first 12 months (3). This initial infection is symptomatic for bronchiolitis and pneumonia in 25% to 40% of infants and young children (5). Fortunately, most infants and young children who are symptomatic for RSV infection recover fully in 8 to 15 days; however, 0.5% to 2% of all infants and young children require hospitalization during their first RSV infection (6).

Infants with pre-existing diseases are at an increased risk of a serious debilitating disease during the RSV season. Bronchopulmonary dysplasia and a congenital heart disease are examples of conditions that increase the risk of serious RSV complications in infants. Other risk factors include pulmonary consolidation on chest radiography, premature birth, and hospitalization during the RSV season (the risk correlates directly with the length of hospital stay) (7). Such environmental factors as exposure to passive cigarette smoke and crowded living conditions also increase the risk of serious RSV complications.

RSV infection is highly predictable on an annual basis. The time of year when RSV outbreaks usually occur is called the RSV season. In the Northern Hemisphere, the RSV season begins in October and ends in April (8).

An epidemiologic survey was conducted in Central Eastern European (CEE) region to characterize the onset, peak, and duration of the RSV season, as well as the incidence and the outcome of hospitalization due to LRTIs caused by RSV in children below one year of age. The main results of this study have been published elsewhere (9). Here we present the data on a selected sample of children below one year of age hospitalized with LRTI (age distribution, risk factors, need for a supportive treatment, and outcome of hospitalization) in two Baltic countries – Lithuania and Estonia.

METHODS

This was a retrospective, cross-sectional, observational, multi-country epidemiologic survey conducted in 12 countries of the CEE region (Bosnia/Herzegovina, Bulgaria, Croatia, the Czech Republic, Estonia, Hungary, Lithuania, Romania, Serbia, Slovakia, Slovenia, and Ukraine). The protocol of the survey was reviewed and approved by national ethics committees. The population studied included children with LRTI, below one year of age, who were admitted to participating hospitals between October 2009 and April 2010 and/or October 2010 and April 2011 (two consecutive RSV seasons).

Eligible subjects were children below one year of age, hospitalized for LRTI (bronchiolitis, pneumonia), and for whom rapid diagnostic test (RDT) for RSV was performed. The following exclusion criteria were applied: children above one year of age and children without information on gestational age, gestational body weight, dates of hospitalization and hospital discharge, and the outcome of hospitalization. For each enrolled patient, informed consent was obtained from the parents, guardians, or legal representatives.

Selection of investigators was based on their prior research experience, expertise in the care of children with LRTI, ability to appropriately perform the survey, and their overall interest in participating in this study. Physicians at Children's Hospital Affiliate of Vilnius University Hospital Santaros Klinikos (<50 beds for infants below one year of age available) and Tallinn Children's Hospital, equipped with 35 beds, participated in this survey.

On the day of hospital discharge or during the first check-up visit after LRTI hospitalization, a physician completed a study questionnaire requesting the following information: demographics (gender, age, gestational age, gestational weight and height), risk factors, patient status at admission, RSV diagnostic procedure, treatment course, and the outcome of disease. The Lithuanian site reported the application of an immunochromatographic method (e.g., BD Directigen RSV, RSV Respi-Strip), whereas the Estonian site applied an immunofluorescence and polymerase chain reaction method to test for RSV infection.

Descriptive statistics were applied for data analysis. Statistical software SAS 9.1.2 (SAS Institute, Cary, NC, USA) was used for statistical data analysis.

RESULTS

In total, 3841 records were collected in the 12 participating countries during both seasons, with 3474 cases (90.4%) fulfilling the case definition (i.e., chil-

dren less than one year of age hospitalized with a diagnosis of bronchiolitis and/or pneumonia within the observational periods). Of this number, 258 case report forms were completed at the Lithuanian site and 289 case report forms were completed at the Estonian site. Among them, four Lithuanian records (1.6%) and 61 Estonian records (21.1%) did not fulfil the case definition of this survey and were not included in the analysis. This resulted in 254 Lithuanian and 228 Estonian documented records fulfilling the definition for an LRTI case, which accounted for 13.9% of the entire survey population. A total of 297 LRTI cases were recorded in season 1 (October 2009–April 2010) and 185 cases were recorded in season 2 (October 2010–April 2011). Table 1 presents the time course of case collection during both seasons in each country separately.

Patient characteristics are summarized in Table 2. Male patients accounted for slightly more than half of all documented LRTI cases (58.3% in Lithuania and 56.1% in Estonia). The majority of hospitalized LRTI patients were less than six months of age. The proportion of premature infants

Table 1. Time course of recorded LRTI cases and RSV-positive cases*

Time period	Lithuania (<i>n</i> = 254)		Estonia (<i>n</i> = 228)		Entire survey population (<i>N</i> = 3474)	
	LRTI	RSV-positive [†]	LRTI	RSV-positive	LRTI	RSV-positive
Season 1	177	108 (61.0)	120	96 (80.0)	1499	567 (37.8)
October 2009	0	0	0	0	8	0
November 2009	2	1 (50.0)	3	1 (33.3)	68	8 (11.8)
December 2009	9	4 (44.4)	1	0	125	13 (10.4)
January 2010	26	13 (50.0)	10	8 (80.0)	215	62 (28.8)
February 2010	63	42 (66.7)	27	23 (85.2)	388	168 (43.3)
March 2010	56	38 (67.9)	47	37 (78.7)	466	209 (44.8)
April 2010	21	10 (47.6)	32	27 (84.4)	229	107 (46.7)
Season 2	77	29 (37.7)	108	103 (95.4)	1975	856 (43.3)
October 2010	1	0	0	0	135	46 (34.1)
November 2010	0	0	0	0	311	109 (35.0)
December 2010	2	0	5	5 (100.0)	419	197 (47.0)
January 2011	9	3 (33.3)	6	6 (100.0)	380	172 (45.3)
February 2011	8	2 (25.0)	10	10 (100.0)	281	117 (41.6)
March 2011	30	10 (33.3)	48	46 (95.8)	276	138 (50.0)
April 11	27	14 (51.9)	39	36 (92.3)	173	77 (44.5)

LRTI – lower respiratory tract infection; RSV – respiratory syncytial virus.

* Values presented are number or number (%).

[†] Percentage of RSV-positive cases in relation to LRTI cases with the RSV rapid diagnostic test.

Table 2. General characteristics of patients*

Patient characteristics	Lithuania (<i>n</i> = 254)	Estonia (<i>n</i> = 228)	Entire survey population (<i>N</i> = 3474)
Sex			
Female	99 (39.0)	92 (40.4)	1409 (40.6)
Male	148 (58.3)	128 (56.1)	2024 (58.3)
Unknown	7 (2.8)	8 (3.5)	41 (1.2)
Age at admission			
0–6 months	192 (75.6)	157 (68.9)	2400 (69.1)
6–12 months	62 (24.4)	71 (31.1)	1074 (30.9)
Gestational age			
≤28 weeks	4 (1.6)	9 (3.9)	121 (3.5)
29–32 weeks	11 (4.3)	6 (2.6)	233 (6.7)
33–36 weeks	16 (6.3)	16 (7.0)	403 (11.6)
≥37 weeks	214 (84.3)	197 (86.4)	2679 (77.1)
Unknown	9 (3.5)	0	38 (1.1)
Mean (SD) birth weight, g	3367 (723)	3291 (776)	2998 (841)
Birth weight			
<1000 g	2 (0.8)	5 (2.2)	101 (2.9)
1000–<1500 g	6 (2.4)	7 (3.1)	176 (5.1)
1500–<2500 g	21 (8.3)	16 (7.0)	482 (13.9)
2500–<4200 g	205 (80.7)	184 (80.7)	2592 (74.6)
>4200 g	20 (7.9)	16 (7.0)	114 (3.3)
Mean (SD) birth height, cm	52 (4)	50 (4)	49 (5)
Concomitant chronic diseases			
Any chronic disease	11 (4.3)	11 (4.8)	591 (17.0)
Congenital heart disease	5 (2.0)	7 (3.1)	166 (4.8)
Bronchopulmonary dysplasia	2 (0.8)	4 (1.8)	145 (4.2)
Neuromuscular disease	1 (0.4)	0	108 (3.1)
Other chronic diseases	10 (3.9)	5 (2.2)	331 (9.5)
RSV prophylaxis	1 (0.4)	0	68 (2.0)

RSV – respiratory syncytial virus.

* All values are *n* (%) unless otherwise stated.

(gestational age of ≤36 weeks) accounted for just over 10% of documented LRTI cases in Lithuania and Estonia; this proportion was almost two times lower than that in the entire survey population (21.8%). The prevalence of concomitant chronic diseases at admission in both Baltic countries was also considerably lower (Table 2) than the rates in the full survey population.

At admission, bronchiolitis was the most common diagnosis of LRTI cases in both countries; pneumonia was diagnosed in about 15% of LRTI cases (Table 3). Considerable differences between

the two countries were observed in the state of consciousness on admission. In Lithuania, 36.6% of hospitalized cases were alert and conscious at admission, whereas in Estonia, 83.3% of cases were conscious at admission.

RSV rapid tests were performed for all documented LRTI cases in Estonia and for 99.6% cases in Lithuania. The aetiology of RSV was confirmed in 87.3% of the tested LRTI cases in Estonia. In Lithuania, the proportion of confirmed RSV cases was lower (54.2%) and was closer to the rates observed in the full survey population (42.4%).

Table 3. Admission diagnosis and performance of an RSV rapid test*

Clinical features on admission	Lithuania (<i>n</i> = 254)	Estonia (<i>n</i> = 228)	Entire survey population (<i>N</i> = 3474)
Admission diagnosis	214 (84.3)	192 (84.2)	1983 (57.1)
Bronchiolitis only			
Pneumonia only	40 (15.7)	35 (15.4)	1183 (34.1)
Bronchiolitis and pneumonia	0	1 (0.4)	308 (8.9)
States of consciousness on admission			
Alert	93 (36.6)	190 (83.3)	1974 (56.8)
Agitated/irritable	120 (47.2)	19 (8.3)	1025 (29.5)
Somnolent	38 (15.0)	18 (7.9)	274 (7.9)
Soporose	2 (0.8)	0	35 (1.0)
Comatose	0	0	15 (0.4)
Unknown	1 (0.4)	1 (0.4)	151 (4.3)
Performance of RSV test	253 (99.6)	228 (100.0)	3354 (96.5)
Confirmed RSV infection	137 (54.2)	199 (87.3)	1423 (42.4)

RSV – respiratory syncytial virus.

* All values are *n* (%) unless otherwise stated.

The mean duration of hospital stay was ten days in Lithuania and seven days in Estonia. In this study, more than 40% of patients with LRTIs in Lithuania and over 30% of cases in Estonia stayed in hospital longer than one week. Intensive care unit (ICU) hospitalization was required for 9.1% of LRTI cases in Lithuania and in 3.1% of cases in Estonia. In LRTI cases transferred to the ICU, the mean duration of stay in the ICU was six days in Lithuania and four days in Estonia (Table 4).

Supplemental oxygen was required for 23.2% of LRTI cases in Lithuania and 31.6% of LRTI cases in Estonia. In LRTI cases with supplemental oxygen administration, the mean duration of oxygen administration was seven days in Lithuania and three days in Estonia. The majority of patients with LRTIs received treatment with bronchodilators (Table 4). In Lithuania, complete recovery at discharge was assessed for 35.8% of LRTI cases and improvement was observed in 62.2% of cases. In Estonia, all

Table 4. Treatment characteristics and outcome of LRTI cases

	Lithuania (<i>n</i> = 254)	Estonia (<i>n</i> = 228)	Entire survey population (<i>N</i> = 3474)
Mean (SD) duration in hospital, days	10 (14)	7 (3)	11 (12)
Duration of hospitalization (categorical), <i>n</i> (%)			
1–3 days	34 (13.4)	24 (10.5)	224 (6.4)
4–7 days	115 (45.3)	126 (55.3)	1360 (39.1)
8–14 days	85 (33.5)	73 (32.0)	1408 (40.5)
≥15 days	19 (7.5)	4 (1.8)	470 (13.5)
Unknown	1 (0.4)	1 (0.4)	12 (0.3)
ICU hospitalization, <i>n</i> (%)	23 (9.1)	7 (3.1)	671 (19.3)
Mean (SD) duration of ICU hospitalization, days	6 (5)	4 (2)	11 (14)

Table 4. (continued)

	Lithuania (n = 254)	Estonia (n = 228)	Entire survey population (N = 3474)
Duration of ICU hospitalization (categorical), n (%)			
1–3 days	13 (5.1)	4 (1.8)	174 (5.0)
4–7 days	4 (1.6)	3 (1.3)	217 (6.2)
8–14 days	3 (1.2)	0	146 (4.2)
≥15days	3 (1.2)	0	114 (4.2)
Right heart failure, n (%)	1 (0.4)	3 (1.3)	76 (2.2)
Occurrence of nosocomial infections, n (%)			
Any nosocomial infection	20 (7.9)	4 (1.8)	213 (6.1)
Nosocomial pneumonia	2 (0.8)	0	49 (1.4)
Nosocomial sepsis	0	0	18 (0.5)
Nosocomial gastrointestinal infection	8 (3.1)	4 (1.8)	133 (3.8)
Other nosocomial infection	11 (4.3)	0	36 (1.0)
Specific nosocomial gastrointestinal infections			
Suspected/confirmed norovirus infection	1 (0.4)	0	12 (0.3)
Suspected/confirmed rotavirus infection	6 (2.4)	4 (1.8)	93 (2.7)
Suspected/confirmed. <i>Clostridium difficile</i> infection	0	0	1 (<0.1)
Supplemental oxygen administration, n (%)	59 (23.2)	72 (31.6)	1563 (45.0)
Mean (SD) duration of supplemental oxygen administration, days	7 (18)	3 (2)	6 (10)
Duration of supplemental oxygen administration (categorical), n (%)			
1–3 days	29 (11.4)	55 (24.1)	763 (22.0)
4–7 days	20 (7.9)	13 (5.7)	474 (13.6)
8–14 days	5 (2.0)	5 (2.0)	186 (5.4)
≥15 days	4 (1.6)	4 (1.6)	111 (3.2)
Use of bronchodilators, n (%)	206 (81.1)	211 (92.5)	2698 (77.7)
Patient outcome at discharge, n (%)			
Complete recovery	91 (35.8)	0	1623 (46.7)
Improvement	158 (62.2)	228 (100.0)	1782 (51.3)
Death	0	0	30 (0.9)
Transfer to other hospital	1 (0.4)	0	21 (0.6)
Unknown	4 (1.6)	0	18 (0.5)

ICU – intensive care unit; LRTI – lower respiratory tract infection.

LRTI cases were improved at discharge, and there were no complete recoveries.

DISCUSSION

Approximately 22% of all episodes of acute LRTIs in children below five years of age are associated with RSV. A substantial proportion of RSV-as-

sociated morbidity occurs in the first year of life, with an incidence in infants that is twice or three times greater than is reported for children below five years overall (10). We present the data describing a selected sample of children younger than one year of age hospitalized with LRTI during two consecutive RSV seasons in two health care centres in Lithuania and Estonia. Out of 482

children below one year of age with LRTI, RSV was confirmed in 87.3% cases at the Estonian site and in 54.2% cases at the Lithuanian site. It should be noted, that different RSV test methods were applied – immunofluorescence and PCR in Estonia and immunochromatographic method in Lithuania.

Well-established disease- and patient-specific risk factors, including congenital heart disease, bronchopulmonary dysplasia, and premature birth, have consistently been found to increase the likelihood of a serious RSV disease. The risk of a serious RSV illness in premature infants is increased if they attend a childcare facility or share a dwelling with multiple siblings or other children. Conditions that compromise handling of respiratory tract secretions, such as congenital abnormalities of the airway and severe neuromuscular disease, are also largely believed to increase the risk of a serious RSV disease (11–13). The parent study reported a more severe course of RSV-related LRTI infection among premature children compared to full-term children (9). In our sample, the established risk factors (i.e., prematurity, concomitant chronic diseases) were relatively less prevalent than in the full survey population.

We observed some differences in the management of enrolled patients between the sites, namely, the duration of hospitalisation and ICU hospitalisation, as well as duration of supplemental oxygen administration. Such findings might be influenced by the severity of the condition of the enrolled patients (e.g., there were considerably fewer alert patients on admission at the Lithuanian site compared to the Estonian site). Also, there were differences in patients' status at discharge – about one-third of discharged patients were completely recovered in Lithuania, whereas all the discharged patients in Estonia were improved but none completely recovered. The latter difference might be related to different local clinical practices in the management of such patients and to the definition of complete recovery.

The results of this study need to be interpreted with caution. Firstly, the data were recorded in a retrospective manner which might have resulted in some recall bias. Secondly, only two health care centres (one in each country) participated in the study, therefore the reported findings might not represent the whole country.

CONCLUSIONS

RSV was highly prevalent among children younger than one year of age hospitalized for LRTIs in Lithuania (54.2%) and Estonia (87.3%). Bronchiolitis was the most common diagnosis in hospitalized patients.

DISCLOSURES

Nijole Drazdienė received research funding and/or support for educational activities from AbbVie, Johnson & Johnson, and Norameda.

Mari Laan served as a consultant and has received support for educational activities from AbbVie and Pfizer.

Jolanta Zaikauskienė is an AbbVie employee and holds AbbVie stocks.

Vytautas Usonis served as a consultant and/or received research funding or support for educational activities from AbbVie, MSD, Roche, Viiv Healthcare, Johnson & Johnson, GSK, and Pfizer.

ACKNOWLEDGEMENTS

The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

Ligita Marozienė of the CRO Biomapas (Lithuania) provided medical writing and editing services. AbbVie provided funding to Biomapas for this work.

Received 18 October 2017

Accepted 9 November 2017

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KŪDIKIŲ, HOSPITALIZUOTŲ DĖL APATINIŲ KVĖPAVIMO TAKŲ INFEKCIJŲ, RESPIRACINIO SINCITINIO VIRUSO PALYGINAMASIS TYRIMAS LIETUVOJE IR ESTIJOJE

Santrauka

Tikslas. Straipsnyje pateikiami vaikų iki 1 metų, hospitalizuotų dėl apatinių kvėpavimo takų infekcijų (toliau – AKTI) Lietuvoje ir Estijoje, tyrimo duomenys.

Metodai. Šis didelės apimties, momentinis stebimasis epidemiologinis tyrimas buvo atliktas 12-oje Centrinės ir Rytų Europos šalių. Tyrime dalyvavo dėl AKTI hospitalizuoti kūdikiai, kuriems atliktas greitas respiracinio sincitinio viruso (toliau – RSV) diagnostinis tyrimas. Išrašymo iš ligoninės arba pirmojo kontrolinio vizito metu gydytojai užpildė tyrimo klausimynus. Lietuvoje RSV diagnostikai taikytas imunochromatografinis tyrimo metodas, o Estijoje – imunofluorescencinis arba polimerazės grandininės reakcijos (PGR) metodai.

Rezultatai. Dviejų iš eilės RSV sezonų laikotarpiu abiejose šalyse stebėti 482 pacientai, atitinkantys AKTI atvejo kriterijus (jaunesni nei 1 metų vaikai, hospitalizuoti dėl bronchiolito ir / arba pneumonijos). Dažniausia diagnozė buvo bronchiolitas (84 %). Lietuvoje ir Estijoje atitinkamai 36,6 ir 83,3% pacientų priėmimo metu buvo sąmoningi, RSV patvirtintas 54,2 ir 87,3 % AKTI pacientų. 9,1 % AKTI pacientų Lietuvoje ir 3,1 % pacientų Estijoje buvo gydomi intensyviosios terapijos skyriuose. Deguonies terapijos prireikė 23,2 % Lietuvos ir 31,6 % Estijos ligonių. Išrašymo metu 35,8 % Lietuvos pacientų buvo visiškai pasveikę, o 62,2 % pacientų būklė buvo pagerėjusi. Visų Estijos pacientų būklė išrašymo metu buvo pagerėjusi, tačiau nei vienas nebuvo visiškai pasveikęs.

Išvada. RSV buvo dažnas tarp kūdikių, hospitalizuotų dėl AKTI Lietuvoje ir Estijoje. Dažniausia hospitalizuotų kūdikių ligos diagnozė – bronchiolitas.

Raktažodžiai: apatinių kvėpavimo takų infekcijos, respiracinis sincitinis virusas, hospitalizacija