

# Hospitalisation of late preterm infants due to lower respiratory tract infections in Lithuania, Latvia, and Estonia: incidence, disease severity, and risk factors

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**Background.** By two years of age, almost all children experience at least one episode of respiratory syncytial virus (RSV) infection, the most common viral cause of hospitalisation due to lower respiratory tract infection (LRTI). We present data on LRTI hospitalisations (with a special focus on RSV), the course of illness, and LRTI hospitalisation risk factors in Lithuania, Latvia, and Estonia.

**Materials and methods.** The analysed data were part of a large multinational study conducted in 23 countries (PONI). LRTI-related hospitalisations were observed during one RSV season for late premature infants (born between 33 weeks and 0 days and 35 weeks and 6 days of gestation)  $\leq 6$  months of age, who did not receive RSV prophylaxis. The potential risk factors and demographics were recorded at study enrolment and at the end of the RSV season. The primary endpoint was hospitalisation due to RSV LRTI; the secondary endpoints included severity, the course and the outcome of LRTI hospitalisations.

**Results.** Out of the 291 infants enrolled in three Baltic states, 19 were hospitalised due to LRTI (6.5%). RSV testing was performed for 14 hospitalised infants; five infants had a positive test for RSV (1.7%). The majority of the hospitalised infants (94.7%) had mild or moderate respiratory illness. Male sex, O<sub>2</sub> dependency after birth, younger maternal age, and furred pets at home were significantly associated with an increased risk for LRTI hospitalisation.

**Conclusions.** During one RSV season, the incidence of LRTI hospitalisations among late preterm infants was 6.5% and the incidence of RSV LRTI hospitalisations was 1.7%.

**Keywords:** preterm infant, hospitalisation, LRTI, RSV

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## INTRODUCTION

Lower respiratory tract infections (LRTIs) are the leading cause of childhood morbidity worldwide (1). Respiratory syncytial virus (RSV) is the most common virus responsible for LRTI-related hospitalisations (2). RSV is the most important cause of childhood mortality from LRTIs after pneumococcal pneumonia and *Haemophilus influenzae* type b infections (3). Preterm infants (born at <37 weeks of gestation) are more susceptible than infants born at term to developing severe LRTIs, irrespective of the degree of prematurity (4).

Respiratory viruses are transmitted from human to human by aerosolised droplets or by direct contact with secretions or contaminated surfaces (5). The incubation period for RSV is 2–8 days (6). RSV infection manifests like many other respiratory tract diseases: early signs include increased body temperature, rhinorrhoea, and decreased appetite (6). RSV infection may manifest as upper respiratory tract infections, otitis media, LRTIs including bronchiolitis and pneumonia, and exacerbations of asthma- or viral-induced wheezing (6). It is unknown why RSV infection develops into lower respiratory tract disease in some children, but there is some evidence that it may be related to a reduced lung function or a genetic predisposition (6).

The peak incidences of respiratory tract diseases are predictable. The outbreaks of certain infections are named according to the causative microorganisms (e.g., “RSV season”, “influenza season”). Certain seasons may vary due to climatic conditions year after year, but usually most are recognised to occur from October to April in the Northern hemisphere (7–9).

Almost all children experience at least one RSV infection by the age of two years (6, 10). Fortunately, the majority of children symptomatic for RSV infection fully recover within 8 to 15 days (11). A systematic review on the burden of RSV infection showed that RSV was associated with 12% to 63% of all acute respiratory infections (ARIs), and with 19% to 81% of all viral ARIs (2).

In the past decade, attempts have been made to assess the burden and risk factors of RSV infection in children, especially preterm infants. The systematic review of 98 published studies identified the following risk factors: male sex, prematu-

rity, age <6 months, birth during the first half of the RSV season, crowding at home/siblings, and day care attendance (2). Risk factors reported in several single-country epidemiologic studies included maternal age, smokers in the house, maternal smoking during pregnancy, no breastfeeding, family members with atopy and ARIs causing hospitalisations in children (7, 12, 13–15).

A large observational epidemiologic study (PONI) evaluated predictors of RSV LRTI hospitalisations in preterm infants (born at 33–35 weeks + 6 days of gestation) in 23 culturally and regionally diverse countries across the northern temperate zone. The multivariable regression models that were conducted showed that the best six-variable predictive model included the following factors: infant age on 1 October (the beginning of RSV season) <3 months, smoking of family members, age of mother at delivery <25 years, presence of children 4–5 years of age in the household, maternal smoking during pregnancy, and day care attendance (8). Here, we present data on LRTI hospitalisation (with a special focus on RSV), the course of illness, and LRTI hospitalisation risk factors in the homogenous population of the Baltic states, which is a subset of the PONI study.

## METHODS

PONI was an observational multi-country, multi-centre epidemiologic study. The study was approved by the national ethics committees and was conducted according to the principles of the Declaration of Helsinki. The selection of study centres was based on their patient population targeted for this study and the ability to collect LRTI hospitalisation data from the admitting hospital(s) in the cases in which infants were hospitalised during the RSV season.

Premature infants who did not receive prophylaxis for RSV infection were observed for hospitalisation due to LRTI infection during one RSV season. Eligible subjects were preterm (33 weeks + 0 days and 35 weeks + 6 days of gestation) infants born after 1 April 2013. Infants who were diagnosed with bronchopulmonary dysplasia, chronic lung disease, and hemodynamically significant congenital heart disease were excluded from the study. Also, infants whose parents intended to

move from the local area before the end of the study and infants who had received RSV prophylaxis were not eligible for inclusion into the study.

Baseline (birth) data of the enrolled infants were collected from medical records and parents/legal representatives by interview at the hospital or by a phone call. The collected data included the eligibility criteria, infant characteristics, perinatal history, and parent demographics. After the RSV season, a second phone call was made for LRTI hospitalisation status and baseline data confirmation. Decisions on hospitalisations were made by individual physicians based on the local practice. Similarly, the decision to test for RSV infection was made according to the local practice of testing using the standard methods. If an infant had been hospitalised for an LRTI, the medical records were retrieved for that hospitalisation and an additional form was completed. If an infant was hospitalised more than once for an infection that was confirmed to be positive for RSV infection, only the hospitalisation with the worst severity (as defined by the supervising physician) was analysed.

The primary endpoint of the study was RSV LRTI hospitalisation during one RSV season (from 1 October 2013 to 30 April 2014). Secondary endpoints included the incidence, severity and the course of LRTI hospitalisations.

The primary objective of the study was to derive predictive factors (risk factors) for RSV LRTI hospitalization based on the observation of whether a predictive factor was present or absent in controls (i.e., infants without an RSV LRTI hospitalization) compared with cases (i.e., infants with an RSV LRTI hospitalization).

Descriptive statistics were used for data analysis. The chi-square test was used for the comparison of qualitative variables and the Mann-Whitney U test was used for the comparison of quantitative variables. Statistical package SPSS 23.0 (IBM Corporation, Armonk, NY, USA) was used to analyse Baltic States data.

## RESULTS

During the study period, 2390 infants across 23 countries met the study criteria and were enrolled. Out of the 204 infants (8.5%) hospitalised for LRTI during the study period, 64 infants (2.7%) were hospitalised for confirmed RSV LRTI. The

RSV hospitalization rate (per 100 infant years) was 4.1 (8).

Of the total enrolment of 2390 infants, six sites in three Baltic States enrolled 291 infants. Baseline sociodemographic and clinical characteristics of the study subjects are summarised in Table 1. There were 19 infants (6.5%) with at least one LRTI hospitalisation. Of these infants, 14 had RSV testing done, with positive tests for RSV in 5 infants (1.7%; Table 2). RSV testing methods included rapid antigen ( $n = 5$ ; 26.3%), indirect immunofluorescence assay (IFA) ( $n = 4$ ; 21.1%) and polymerase chain reaction (PCR) ( $n = 3$ ; 15.8%). Data on RSV testing method were missing for two infants in Latvia. The proportion of hospitalised infants with RSV testing performed ranged from 50% in Latvia to 100% in Estonia. The main reason for not performing RSV testing in hospitalised infants was reported as “not standard practice” (three cases in Latvia and one case in Lithuania).

The duration of LRTI hospitalisation ranged from 3 to 16 days (mean, 7.1 days) and the mean duration of respiratory illness symptoms was 9.6 days. Eight infants (42.1%) required oxygen supplementation (4.13 days on average). One infant was admitted to the paediatric intensive care unit/neonatal intensive care unit. Mechanical ventilation was not required for any of the hospitalised infants.

According to investigator assessment, one case of respiratory illness was severe and ten cases were of moderate severity (Table 2). The most common symptoms observed for the hospitalised infants included rhinorrhoea (73.7%), cough (68.4%), and tachypnea (52.6%). Wheezing was reported for all infants with confirmed RSV infection. In two hospitalised infants, viral infections other than RSV were diagnosed. One infant had parainfluenza 1 virus, while a causative virus was not identified in another infant.

The most common medical interventions during LRTI hospitalisation were nasopharyngeal suctioning (52.6%) and fluids maintenance (47.4%). Inhaled and systemic corticosteroids (47.4%) and  $\beta$ -2 agonists (36.8%) were the most frequently prescribed pharmacologic therapies. None of the hospitalised infants received aerosolised recombinant human DNase, aerosolised ribavirin, He-O<sub>2</sub> gas mixtures, nitric oxide, or extracorporeal membrane oxygenation therapies.

**Table 1.** Baseline sociodemographics and clinical characteristics of study subjects<sup>a</sup>

| Characteristics                                  | Total<br>( <i>N</i> = 291) | Country                      |                               |                            | Hospitalisation status                   |   |  |
|--|----------------------------|------------------------------|-------------------------------|----------------------------|--|---|--|
|  |                            | Estonia<br>( <i>n</i> = 105) | Lithuania<br>( <i>n</i> = 96) | Latvia<br>( <i>n</i> = 90) | LRTI hospitalisation<br>( <i>n</i> = 19) | RSV LRTI hospitalisation<br>( <i>n</i> = 5) | No LRTI hospitalisation<br>( <i>n</i> = 272) |
| Infant characteristics                           |                            |                              |                               |                            |  |   |  |
| Male sex, <i>n</i> (%)                           | 164<br>(56.4)              | 56 (53.3)                    | 56 (58.3)                     | 52 (57.8)                  | 17 (89.5)                                | 5 (100.0)                                   | 147 (54.0)*                                  |
| Mean (SD) birthweight, g                         | 2220.8<br>(464.7)          | 2331.3<br>(418.5)            | 2112.3<br>(494.7)             | 2207.6<br>(458.9)          | 2091.8<br>(594.9)                        | 2061.0<br>(472.7)                           | 2229.8<br>(454.3)                            |
| Multiple-birth infants, <i>n</i> (%)             | 106<br>(36.4)              | 21 (20.0)                    | 46 (47.9)                     | 39 (43.3)                  | 10 (52.6)                                | 3 (60.00)                                   | 96 (35.3)                                    |
| Gestational age, weeks                           |                            |                              |                               |                            |  |   |  |
| Mean (SD)  | 34.4 (0.8)                 | 34.6 (0.8)                   | 34.1 (0.8)                    | 34.5<br>(0.8)              | 34.3 (0.9)                               | 34.2 (1.1)                                  | 34.4 (0.8)                                   |
| Missing cases, <i>n</i> (%)                      | 61 (21.0)                  | 10 (9.5)                     | 6 (6.2)                       | 45 (50)                    | 4 (21.1)                                 | 2 (40.0)                                    | 57 (21.0)                                    |
| Infants born before 1 October <i>n</i> (%)       | 152<br>(52.2)              | 56 (53.3)                    | 48 (50.0)                     | 48 (53.3)                  | 9 (47.4)                                 | 2 (40.0)                                    | 143 (52.6)                                   |
| Age ≤3 months on 1 October, <i>n</i> (%)         | 219<br>(75.3)              | 81 (77.1)                    | 71 (74.0)                     | 67 (74.4)                  | 16 (84.2)                                | 5 (100.0)                                   | 203 (74.6)                                   |
| Vaginal delivery, <i>n</i> (%)                   | 159<br>(54.6)              | 64 (61.0)                    | 49 (51.0)                     | 46 (51.1)                  | 11 (57.9)                                | 3 (60.0)                                    | 148 (54.4)                                   |
| Assisted fertilization, <i>n</i> (%)             | 28 (9.6)                   | 12 (11.4)                    | 8 (8.3)                       | 8 (8.9)                    | 1 (5.3)                                  | 0 (0.0)                                     | 27 (9.9)                                     |
| Comorbidities, <i>n</i> (%)                      |                            |                              |                               |                            |  |   |  |
| Any  | 220<br>(75.6)              | 52 (49.5)                    | 78 (81.3)                     | 90<br>(100.0)              | 13 (68.4)                                | 5 (100.0)                                   | 206 (75.7)                                   |
| Neonatal jaundice                                | 108<br>(22.8)              | 21 (17.1)                    | 32 (23.0)                     | 55 (25.9)                  | 6 (20.0)                                 | 4 (33.3)                                    | 102 (23.0)                                   |
| Respiratory distress syndrome                    | 81 (17.1)                  | 19 (15.4)                    | 50 (36.0)                     | 12 (5.7)                   | 2 (6.7)                                  | 1 (8.3)                                     | 79 (17.8)                                    |
| Non-hsCHD diagnosis                              | 3 (1.0)                    | 1 (1.0)                      | 0 (0.0)                       | 2 (2.2)                    | 1 (5.3)                                  | 0 (0.0)                                     | 2 (0.7)                                      |
| Initial hospital stay <7 days, <i>n</i> (%)      | 28 (9.6)                   | 15 (14.3)                    | 4 (4.2)                       | 9 (10.0)                   | 1 (5.3)                                  | 0 (0.0)                                     | 27 (9.9)                                     |
| Resuscitation required, <i>n</i> (%)             | 25 (8.6)                   | 6 (5.7)                      | 4 (4.2)                       | 15 (16.7)                  | 2 (10.5)                                 | 0 (0.0)                                     | 23 (8.5)                                     |
| Infant-assisted ventilation (CPAP), <i>n</i> (%) | 147<br>(50.5)              | 39 (37.1)                    | 64 (66.7)                     | 44 (48.9)                  | 13 (68.4)                                | 3 (60.0)                                    | 134 (49.3)                                   |
| Infant O <sub>2</sub> dependency, <i>n</i> (%)   | 113<br>(38.8)              | 23 (21.9)                    | 41 (42.7)                     | 49 (54.4)                  | 13 (68.4)                                | 2 (40.0)                                    | 100 (36.8)*                                  |
| Infant surfactant use, <i>n</i> (%)              | 12 (4.1)                   | 6 (5.7)                      | 2 (2.1)                       | 4 (4.4)                    | 1 (5.3)                                  | 0 (0.0)                                     | 11 (4.0)                                     |

**Table 1.** (continued)

| Characteristics  | Total<br>(N = 291) | Country              |                       |                    | Hospitalisation status                |   |  |
|--|--------------------|----------------------|-----------------------|--------------------|---------------------------------------|---|--|
|  |                    | Estonia<br>(n = 105) | Lithuania<br>(n = 96) | Latvia<br>(n = 90) | LRTI hospi-<br>talisation<br>(n = 19) | RSV LRTI<br>hospitali-<br>sation<br>(n = 5) | No LRTI<br>hospitalisa-<br>tion<br>(n = 272) |
| <i>Maternal/family charac-<br/>teristics</i>                           |                    |                      |                       |                    |                                       |   |  |
| Mean (SD) maternal age<br>at delivery, years                           | 30.4 (5.5)         | 31.3 (5.5)           | 30.3 (5.1)            | 29.5<br>(6.0)      | 27.3 (4.3)                            | 26.0 (6.5)                                  | 30.6 (5.6)*                                  |
| Maternal age ≤25 years,<br>n (%)                                       | 53 (18.2)          | 16 (15.2)            | 14 (14.6)             | 23 (25.6)          | 7 (36.8)                              | 3 (60.0)**                                  | 46 (16.9)*                                   |
| Higher education of<br>mother, n (%)                                   | 176<br>(60.5)      | 55 (52.4)            | 66 (68.8)             | 55 (61.1)          | 10 (52.6)                             | 1 (20.0)                                    | 116 (61.0)                                   |
| Smoking during preg-<br>nancy, n (%)                                   | 21 (7.2)           | 11 (10.5)            | 4 (4.2)               | 6 (6.7)            | 3 (15.8)                              | 1 (20.0)                                    | 18 (6.6)                                     |
| Atopy/allergy in first-de-<br>gree family member, n<br>(%)             | 280<br>(96.2)      | 104<br>(99.0)        | 95 (99.0)             | 81 (90.0)          | 18 (94.7)                             | 5 (100.0)                                   | 262 (96.3)                                   |
| <i>Environmental charac-<br/>teristics</i>                             |                    |                      |                       |                    |                                       |   |  |
| Breastfed, n (%)   | 281<br>(96.6)      | 103<br>(98.1)        | 94 (97.9)             | 84 (93.3)          | 17 (89.5)                             | 5 (100.0)                                   | 264 (97.1)                                   |
| Other children <18 years<br>living in the household,<br>n (%)          | 140<br>(48.1)      | 77 (73.3)            | 33 (34.4)             | 30 (33.3)          | 10 (52.6)                             | 2 (40.0)                                    | 130 (47.8)                                   |
| Smoker living with in-<br>fant, n (%)                                  | 100<br>(34.4)      | 40 (38.1)            | 27 (28.1)             | 33 (36.7)          | 10 (52.6)                             | 4 (80.0)**                                  | 90 (33.1)                                    |
| Number of adults >2 in<br>the household, n (%)                         | 59 (20.3)          | 17 (16.2)            | 15 (15.6)             | 27 (30.0)          | 4 (21.1)                              | 2 (40.0)                                    | 55 (20.2)                                    |
| Residents >4 in the<br>household                                       | 86 (29.6)          | 48 (45.7)            | 19 (19.8)             | 19 (21.1)          | 5 (26.3)                              | 1 (20.0)                                    | 81 (29.8)                                    |
| Presence of furred pets at<br>home, n (%)                              | 132<br>(45.4)      | 51 (48.6)            | 36 (37.5)             | 45 (50.6)          | 13 (68.4)                             | 4 (80.0)                                    | 119 (43.8)*                                  |
| Day care attendance of<br>the subject, n (%)                           | 1 (0.3)            | 1 (1.0)              | 0 (0.0)               | 0 (0.0)            | 0 (0.0)                               | 0 (0.0)                                     | 1 (0.4)                                      |
| Day care attendance of<br>other children in the<br>household,<br>n (%) | 67 (23.0)          | 32 (30.5)            | 12 (12.5)             | 23 (25.6)          | 6 (31.6)                              | 1 (20.0)                                    | 61 (22.4)                                    |

\*  $p < 0.05$  between LRTI hospitalisation and no LRTI hospitalisation cases.

\*\*  $p < 0.05$  between RSV LRTI hospitalisation and no LRTI hospitalisation cases.

CPAP – continuous positive airway pressure; LRTI – lower respiratory tract infection; non-hsCHD – non-hemodynamically significant congenital heart disease; RSV – respiratory syncytial virus; SD – standard deviation.

<sup>a</sup> Percentages were calculated using the total number of the corresponding columns.

**Table 2.** Characteristics of LRTI hospitalisations<sup>a</sup>

| Characteristics  | Total (N = 19) | Confirmed RSV (n = 5) | Estonia (n = 4) | Lithuania (n = 7) | Latvia (n = 8) |
|--|----------------|-----------------------|-----------------|-------------------|----------------|
| Prescribed RSV test, n (%)                               | 14 (73.7)      | –                     | 4 (100.0)       | 6 (85.7)          | 4 (50.0)       |
| Positive result of RSV test, n (%)                       | 5 (26.3)       | –                     | 1 (25.0)        | 2 (28.6)          | 2 (25.0)       |
| RSV method <sup>b</sup> , n (%)                          |                |                       |                 |                   |                |
| Rapid antigen  | 5 (26.3)       | 1 (20.0)              | 1 (25.0)        | 4 (57.1)          | –              |
| IFA  | 4 (21.1)       | 2 (40.0)              | 2 (50.0)        | –                 | 2 (25.0)       |
| PCR  | 3 (15.8)       | 2 (40.0)              | 1 (25.0)        | 2 (28.6)          | –              |
| Severity of illness, n (%)                               |                |                       |                 |                   |                |
| Severe   | 1 (5.3)        | 1 (20.0)              | –               | 1 (14.3)          | –              |
| Moderate   | 10 (52.6)      | 4 (80.0)              | 3 (75.0)        | 5 (71.4)          | 2 (25.0)       |
| Mild   | 8 (42.1)       | –                     | 1 (25.0)        | 1 (14.3)          | 6 (75.0)       |
| Mean (SD) duration of hospitalisation, days              | 7.1 (3.1)      | 8.4 (4.2)             | 7.5 (3.0)       | 8.1 (4.2)         | 6.0 (1.6)      |
| Mean (SD) duration of respiratory illness symptoms, days | 9.6 (3.8)      | 12.2 (4.7)            | 8.0 (3.5)       | 11.5 (4.7)        | 8.5 (0.6)      |
| Requirement of oxygen supplementation, n (%)             | 8 (42.1)       | 3 (60.0)              | –               | 6 (85.7)          | 2 (25.0)       |
| Admittance to PICU/NICU, n (%)                           | 1 (5.3)        | 1 (20.0)              | –               | 1 (14.3)          | –              |
| Fever >38.8°C, n (%)                                     | 1 (5.3)        | 0 (0.0)               | 1 (25.0)        | –                 | –              |
| Presence of symptoms, n (%)                              |                |                       |                 |                   |                |
| Cough  | 13 (68.4)      | 5 (100.0)             | 4 (100.0)       | 6 (85.7)          | 3 (37.5)       |
| Rhinorrhea   | 14 (73.7)      | 5 (100.0)             | 4 (100.0)       | 6 (85.7)          | 4 (50.0)       |
| Hoarseness   | 2 (10.5)       | 1 (20.0)              | –               | 2 (28.6)          | –              |
| Wheezing   | 8 (42.1)       | 5 (100.0)*            | 3 (75.0)        | 3 (42.9)          | 2 (25.0)       |
| Retractions  | 7 (36.8)       | 3 (60.0)              | 1 (25.0)        | 6 (85.7)          | –              |
| Tachypnea  | 10 (52.6)      | 5 (100.0)             | 1 (25.0)        | 6 (85.7)          | 3 (37.5)       |
| Cyanosis   | 2 (10.5)       | 1 (20.0)              | –               | 2 (28.6)          | –              |
| Other viral infections, n (%)                            | 2 (10.5)       | –                     | 1 (25.0)        | –                 | 1 (12.5)       |
| Treatment  |                |                       |                 |                   |                |
| β-2 agonists   | 7 (36.8)       | 4 (80.0)              | 4 (100.0)       | 1 (14.3)          | 2 (25.0)       |
| Racemic epinephrine                                      | 1 (5.3)        | 1 (20.0)              | –               | 1 (14.3)          | –              |
| Aerosolised recombinant human DNase                      | –              | –                     | –               | –                 | –              |
| Inhaled and systemic corticosteroids                     | 9 (47.4)       | 4 (80.0)              | 4 (100.0)       | 1 (14.3)          | 4 (50.0)       |
| Aerosolised ribavirin                                    | –              | –                     | –               | –                 | –              |
| Nasopharyngeal suctioning                                | 10 (52.6)      | 4 (80.0)              | 1 (25.0)        | 5 (71.4)          | 4 (50.0)       |
| He-O <sub>2</sub> gas mixtures                           | –              | –                     | –               | –                 | –              |
| Nitric oxide   | –              | –                     | –               | –                 | –              |

\*  $p < 0.05$  between RSV LRTI hospitalisation and LRTI hospitalisation cases.

IFA – indirect immunofluorescence assay; PCR – polymerase chain reaction; PICU/NICU – paediatric intensive care unit/neonatal intensive care unit; RSV – respiratory syncytial virus; SD – standard deviation.

<sup>a</sup> Percentages were calculated using the total number of the corresponding columns;

<sup>b</sup> Data on the RSV method were missing for two subjects in Latvia.

**Table 2.** Characteristics of LRTI hospitalisations<sup>a</sup> (*continued*)

| Characteristics                     | Total<br>(N = 19) | Confirmed<br>RSV (n = 5) | Estonia<br>(n = 4) | Lithuania<br>(n = 7) | Latvia (n = 8) |
|-------------------------------------|-------------------|--------------------------|--------------------|----------------------|----------------|
| Extracorporeal membrane oxygenation | –                 | –                        | –                  | –                    | –              |
| Nebulised hypertonic saline         | 3 (15.8)          | 1 (20.0)                 | 1 (25.0)           | –                    | 2 (25.0)       |
| Fluids maintenance                  | 9 (47.4)          | 4 (80.0)                 | 2 (50.0)           | 5 (71.4)             | 2 (25.0)       |

IFA, indirect immunofluorescence assay; LRTI, lower respiratory tract infection; PCR, polymerase chain reaction; PICU/NICU, pediatric intensive care unit/neonatal intensive care unit; RSV, respiratory syncytial virus; SD, standard deviation.

<sup>a</sup> Percentages were calculated using the total number of the corresponding columns.

The majority of infant, maternal, family, and environmental characteristics did not differ between infants hospitalised for LRTI and non-hospitalised infants (Table 1). Infants with confirmed RSV LRTI hospitalisation had younger mothers and lived with a smoker more frequently than non-hospitalised infants. The following characteristics were more common among LRTI hospitalised infants and were identified as risk factors for LRTI hospitalisation: male sex (OR, 7.23; 95% confidence interval (CI), 1.64–31.89), O<sub>2</sub> dependency after birth (OR, 3.73; 95% CI, 1.37–10.11), maternal age <25 years (OR, 2.87; 95% CI, 1.07–7.67), and presence of furred pets at home (OR, 2.77; 95% CI, 1.02–7.50).

## DISCUSSION

The analysed data were part of a large multinational study conducted in the Northern hemisphere. The three Baltic states are often analysed as one area due to similar history, traditions, and socioeconomic situation. Therefore the Baltic population was more homogenous than that of the entire PONI study population.

The incidence of LRTI hospitalisations in the Baltic states was 6.5%, which is slightly lower than the incidence observed in the total PONI population (8.5%) (8), as well as in the RISK study (7.9%) conducted in late preterm (33–35 weeks gestational age) infants (14). Of 19 hospitalised infants, respiratory illness was severe in one case and moderately severe in ten cases. The mean duration of LRTI hospitalisations was seven days, while respiratory symptoms lasted for a mean of 9.6 days. Nearly half of the hospitalised infants required oxygen supplementation; however, none required mechanical ventilation. The incidence of laboratory-confirmed RSV LRTI hospi-

talizations was 1.7% (five cases) in the Baltic states, which was 1.5-fold lower than in the total PONI population (2.7%) (8). Other studies reported incidences of RSV LRTI hospitalisation in preterm infants ranging from 3% to 5% (14–16).

In this study, investigators applied RSV testing according to the standard practices of the hospitals. RSV testing was not conducted for 26.3% of the infants hospitalised with LRTI in the Baltic states compared with 19.6% of infants in the total PONI population (8). Testing for RSV was not conducted in 16.6% of infants hospitalised for respiratory disease in the RISK study (14).

In the PONI study, factors associated with an increased risk of RSV-related LRTI hospitalisation were smoking of family members, a diagnosis of non-hemodynamically significant congenital heart disease, maternal age of ≤25 years at delivery, low maternal educational level, household presence of children aged 4 to 5 years, age ≤3 months at the beginning of an RSV season and presence of paternal atopy (8). Due to a very low number of infants with confirmed RSV infection and hospitalisation due to LRTI, we were not able to conduct a multivariable logistic regression analysis to check if the same risk factors were valid in the relatively homogenous population of the Baltic states. Examination of bivariate associations revealed that male sex, infant O<sub>2</sub> dependence after birth, young maternal age at delivery, and furred pets at home were risk factors for LRTI hospitalisation irrespective of the viral cause. Infants with confirmed RSV infection had younger mothers and lived with smokers more frequently than non-hospitalised infants.

Differences in the risk factors identified in the total heterogeneous PONI population and in its Baltic subpopulation might be explained by

sociodemographic, cultural, and healthcare diversities. For example, there were differences in the prevalence of some characteristics between the infants in the Baltic states compared with the entire PONI population: vaginal delivery (54.6% vs 37.8%, respectively), assisted fertilisation (9.6% vs 18.1%), any comorbidity (75.6% vs 49.7%), higher education of the mother (60.5% vs 15.2%), family history of atopy (96.2% vs 38.7%), breastfeeding (96.6% vs 73.1%), household size >4 individuals (29.6% vs 15.4%), and day care attendance (0.3% vs 13.5%).

A variety of risk factors were reported in studies conducted in different countries. For example, young maternal age and smokers living with an infant were risk factors for RSV hospitalisation in Spain (17–18), the Netherlands (15), and Italy (19). On the other hand, older maternal age was a risk factor in a Russian study (20). Male sex was considered to be a risk factor for RSV LRTI hospitalisation in Spain (13), Canada (16), and Denmark (2), whereas it was not a risk factor in several other studies (15, 17, 20). Contradictory results have been reported on the presence of furred pets at home: the FLIP study confirmed that furred pets are a risk factor for RSV hospitalisation (13), whereas the RISK study found no association between furred pets at home and a risk for RSV hospitalisation (14). O<sub>2</sub> dependency after birth was not evaluated in other published studies.

Younger infant age and crowded living conditions were determined to be risk factors for RSV hospitalisation in many studies (7, 10, 13–14, 16, 18–19, 21); however, these characteristics were not significant risk factors in our analysis.

Breastfeeding and family history of atopy are important determinants of infant health. Infants who were not breastfed or who were breastfed for <2 months had a higher risk for RSV hospitalisation (13–15, 19). Atopy/allergy of a first-degree family member also was associated with a higher RSV hospitalisation risk (14–15, 21). In our study, the majority of infants were breastfed (96.6%) for any period of time and had a family member with atopy/allergy (96.2%); the prevalence of those factors did not differ between LRTI hospitalised and non-hospitalised infants.

## CONCLUSIONS

In the Baltic states, the incidence of LRTI hospitalisations during one RSV season among late

preterm infants was 6.5%. The incidence of RSV LRTI hospitalisations was 1.7%. The majority of the hospitalised infants (94.7%) had mild or moderate respiratory illness. Male sex, O<sub>2</sub> dependency after birth, younger maternal age, and presence of furred pets at home were significantly associated with an increased risk for LRTI hospitalisation.

## DISCLOSURES

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

Rasa Tamelienė received support for educational activities from AbbVie.

Daiga Kviluna served as a consultant and has received support for educational activities from AbbVie.

Pille Saik has nothing to disclose.

Ervin Saik has nothing to disclose.

Jolanta Zaikauskienė is an AbbVie employee and holds AbbVie stocks.

## 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 26 March 2018

Accepted 31 May 2018

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**NEIŠNEŠIOTŲ KŪDIKIŲ HOSPITALIZACIJA  
DĖL APATINIŲ KVĖPAVIMO TAKŲ INFEKCIJŲ  
LIETUVOJE, LATVIJOJE IR ESTIJOJE:  
PAPLITIMAS, LIGOS SUNKUMAS IR RIZIKOS  
VEIKSNIAI**

*Santrauka*

**Įvadas.** Beveik visi vaikai iki dvejų metų bent vieną kartą susergera respiracinio sincitinio viruso (RSV) sukelta infekcija. RSV yra dažniausia vaikų hospitalizacijos dėl apatinių kvėpavimo takų infekcijų (AKTI) priežastis. Pateikiame duomenis apie AKTI hospitalizacijų (akcentuojant RSV atvejus) dažnį, ligos eigą ir rizikos veiksnius Lietuvoje, Latvijoje ir Estijoje.

**Metodai.** Analizuota dalis duomenų, kurie buvo surinkti per tarptautinį tyrimą, kurį vykdė 23 šalys (PONI). Neišnešiotų kūdikių (nuo 33 savaičių ir 0 dienų iki 35 savaičių ir 6 dienų gestacinio amžiaus), ne vyresnių nei 6 mėn., kuriems nebuvo skirta RSV imunoprofi-

laktika, hospitalizacijos dėl AKTI buvo registruojamos vieno RSV sezono metu. Informacija apie galimus rizikos veiksnius ir demografiniai duomenys buvo renkami per tyrimą ir RSV sezono pabaigoje. Pagrindinis vertinimo kriterijus buvo hospitalizacija dėl RSV AKTI, antrinis – AKTI sunkumas, eiga ir baigtis.

**Rezultatai.** Trijose Baltijos šalyse tyrime dalyvavo 291 kūdikis, iš jų 19 buvo hospitalizuoti dėl AKTI (6,5 %). RSV testas atliktas 14 hospitalizuotų kūdikių, 5 kūdikių RSV testo rezultatai buvo teigiami (1,7 %). Daugumos (94,7 %) hospitalizuotų kūdikių būklė buvo įvertinta kaip lengva ar vidutinio sunkumo. Vyrishka lytis, O<sub>2</sub> terapijos būtinybė po gimimo, jaunesnis motinos amžius ir kailiniai naminiai gyvūnai buvo reikšmingai susiję su didesne kūdikių, sergančių AKTI, hospitalizacijos rizika.

**Išvados.** Per vieną RSV sezoną hospitalizacijos dėl AKTI sudarė 6,5 %, o hospitalizacijos dėl RSV sukeltų AKTI – 1,7 %.

**Raktažodžiai:** neišnešioti kūdikiai, hospitalizacija, AKTI, RSV