

Respiratory infections in very low gestational age infants: a population-based cohort study in Estonia

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Abstract

Background: There is little comparative information available on the occurrence of respiratory infections (RI) in infants with different degrees of maturity at birth. We aimed to determine the rate and characteristics of RI during the first two years of life in very low gestational age (VLGA) infants compared with the control cohort of full-term (FT) infants and to identify the risk factors for unfavourable outcomes of RI.

Methods: The study was a part of a population-based prospective cohort study of VLGA infants born at 22-31 gestational weeks in 2007 in Estonia. At the corrected age of 2 years, surviving 155 VLGA infants were compared with their individually matched FT controls. Perinatal variables were recorded prospectively whereas episodes and characteristics of RI were assessed retrospectively by parental interviews. A logistic regression model was used to test risk factors for unfavourable outcomes (wheezing, recurrent wheezing, and hospitalisation) of RI.

Results: The frequency of RI was similar in VLGA and FT infants. However, wheezing as well as recurrent wheezing due to RI was more frequent in VLGA than in FT infants, 34% vs. 21% (OR: 1.9; 95% CI: 1.1-3.2) and 14% vs. 5% (OR: 3.3; 95% CI: 1.4-7.1), respectively. During RI, VLGA infants also needed more hospitalisations (33% vs. 18%; OR: 2.3; 95% CI: 1.3-3.9). There was no significant difference between VLGA infants without bronchopulmonary dysplasia (BPD) compared with FT infants in wheezing and recurrent wheezing. BPD was the main risk factor for all unfavourable outcomes of RI.

Conclusions: The frequency of RI in VLGA and FT infants is similar but BPD is more likely than prematurity in itself to predispose VLGA infants to a more severe clinical course of RI.

Keywords

Bronchopulmonary dysplasia, hospitalisation, population-based study, respiratory infections, very low gestational age infants, wheezing.

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Introduction

Acute respiratory infections (RI) are one of the most frequent health problems in young children. It has been shown that during the first years of life a normal child may present up to five to eight annual diseases due to RI [1, 2]. Several social and environmental factors, such as attendance of day care, family size, air pollution, parental smoking, and home dampness have been suggested to predispose to recurrent RI [3]. Wheezing commonly accompanies RI during the first years of life [4, 5]. Recurrent or serious RI, especially with wheezing episodes, during the critical period of lung development in the first years of life, may lead to an increased risk of asthma later in life [6]. Although many RI are not severe, they contribute to a poorer health-related quality of life for children, to absenteeism from work for parents, and to increased costs for society [7, 8].

While acute respiratory morbidity in full-term (FT) infants is relatively well studied, data on preterm infants during the post-surfactant era and among different gestational age (GA) groups are scarce. Previous studies have shown that compared with FT infants, premature infants are more susceptible to acute RI having more wheezing episodes and hospital readmissions due to respiratory problems in the first two years of life [9, 10]. Moreover, they are more likely to die from acute lower respiratory tract infections than other infants [11]. Although some data are available comparing acute respiratory morbidity in premature and FT infants from the same recruitment area and time period [12, 13], to our knowledge, no nationwide population-based studies have been published.

In Estonia, a Baltic country with a population of 1.3 million and health care expenditure (in terms of purchasing power parity per capita) three times lower than in countries that were members of the European Union before 2004 [14], the survival of very low

gestational age (VLGA) infants born before 32 gestational weeks (GW) has improved dramatically due to improvements in perinatal care. Depending on GA, 51% and 93% of those born at 22-25 and 26-31 GW, respectively, survived in 2007 [15]. To evaluate the effect of recent changes in perinatal care on respiratory morbidity we conducted a population-based study with the primary aims to determine the rate and the characteristics of RI during the first two years of life in VLGA infants compared with their FT controls and to identify risk factors associated with unfavourable outcomes of RI.

Methods

Study design

The present study was seeded into the nationwide cohort study of VLGA infants born from 1 January 2007 to 31 December 2007 in Estonia. The details of that study are presented elsewhere [16].

Patients and controls

Altogether 187 VLGA (22⁺⁰ to 31⁺⁶ GW) infants were born alive and 158 (84.5%) survived until hospital discharge. Two children died before 2 years of age (one as a consequence of severe bronchopulmonary dysplasia [BPD], and the other as a consequence of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency) and one had moved abroad. The remaining 155 infants underwent an assessment at the corrected age of 2 years.

For each surviving VLGA infant, two matched FT (≥ 37 GW) infants were identified from maternity ward databases using the following inclusion criteria: 1) no requirement for medical interference during the first week of life; 2) born in the same geographical area; 3) having the same gender and nationality; and 4) born as the first or the second infant after the expected date of birth of the VLGA infant. As a rule, for each VLGA infant the first FT control infant was selected. However, if the parents of the first FT control infant were not accessible, the second control was approached. In two cases, both families of identified control FT infants refused to participate in the follow-up. A total of 153 FT infants were enrolled in the study.

Monitoring of patients and data collection

Perinatal data of VLGA infants were collected prospectively. At the corrected age of 24 (± 1)

months, the families of VLGA and FT infants were invited to a study centre for physical and developmental assessment. Structured parental interviews were performed and socio-demographic and environmental exposures (parental age and education, family structure and income, number of siblings in the same household, duration of breastfeeding, and age at day care attendance) as well as the presence of respiratory illnesses during the first two years of life were recorded. The parents or legal guardians were specifically asked about the infant's acute respiratory morbidity, wheezing episodes during RI, overall hospitalisations and hospitalisations due to RI, and the number of antibiotic courses prescribed in total and for RI. All RI cases treated at home were identified only by parental report whereas parental reports of hospitalisations were checked against the hospital databases to capture all admissions and their reasons.

Definitions

Infants whose birth weight was below the 10th percentile for their GA according to the Fenton Intra-uterine Growth Curves [17] were considered small for GA. BPD was diagnosed if there was oxygen dependency at 36 weeks' postmenstrual age [18].

All RI cases were identified by parental reports using the following criteria: 1) episodes of illness characterised by nasal congestion, rhinorrhea, cough, sore throat, fever, and/or wheeze; or 2) physician-diagnosed upper or lower (bronchitis, bronchiolitis, pneumonia) respiratory tract infections or acute otitis media. RI with gastrointestinal symptoms were included whereas gastroenteritis (e.g. rotavirus, norovirus) not accompanying RI were excluded. Recurrent RI were defined as the presence of a higher number of RI episodes than the population's mean value. Wheezing was defined as an episodic wheeze due to RI whereas recurrent wheezing (RW) was defined as three or more episodes of wheezing due to RI during the study period. Wheezing, RW, and hospitalisation due to RI were considered to be unfavourable outcomes of RI.

Socioeconomic status of the parents included: 1) educational level, categorised as low (no formal education or primary education), middle (secondary education), or high (higher professional education or university degree); and 2) monthly income per family member, categorised as low (< 2,000 Estonian crowns/<128 EUR), medium (2,000-10,000 Estonian crowns/128-641 EUR), or high (> 10,000 Estonian crowns/>641 EUR).

Age at day care attendance was defined as chronological age at the first entry into day care centre. Breastfeeding included both exclusive and/or partial breastfeeding regardless of the amount. Neurodevelopmental impairment and growth restriction at the infants' corrected age of 2 years are detailed elsewhere [16].

Statistical analysis

Statistical analysis was performed using the statistical package Stata 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Associations between the characteristics of RI and maturity at birth were assessed by Poisson regression and presented as incidence rate ratios (IRR) with 95% confidence intervals (CI) or by conditional logistic regression and odds ratios (OR) depending on the type of variables. The distributions of the reasons for hospitalisations were compared by Fisher exact test. Uni- and multivariate logistic regression analyses were used in risk factor analysis for unfavourable outcomes of RI as follows: selected risk factors were first added in the univariate model and only statistically significant variables ($p < 0.05$) were then included in the multivariate model. The following risk factors were tested: maternal age and education, family income and size, infant gender, GA, birth weight < 10th percentile, multiple birth, BPD, duration of breastfeeding, age at day care attendance, as well as weight < 10th percentile and neurodevelopmental impairment at the corrected age of 2 years. The analysis described above was carried out in both study cohorts as a whole as well as only for VLGA infants whereas the same selected risk factors were used.

Ethics

The study was approved by the Ethics Review Committee on Human Research of the University of Tartu and parent(s) or legal guardian(s) signed informed consent prior to inclusion.

Results

Patients' demographics

The background characteristics of VLGA infants and their FT controls are summarised in **Tab. 1** and **Tab. 2**. Three VLGA infants had a congenital anomaly or a syndrome of clinical significance (Tetralogy of Fallot, congenital laryngeal stenosis,

Table 1. Perinatal variables and morbidity of very low gestational age (VLGA; 22⁺⁰ to 31⁺⁶ gestational weeks) and full-term (FT; 37⁺⁰ to 41⁺⁶ gestational weeks) infants.

	VLGA infants (n = 155)	FT infants (n = 153)	OR (95% CI) or P-value for comparing means
Perinatal variables			
Antenatal steroids, n (%)	128 (83)	0	NA
Multiple births, n (%)	38 (25)	2 (1)	24.5 (5.8-103.7)
Gestational age, mean (95% CI), weeks	28.8 (28.4-29.1)	39.6 (39.4-39.7)	< 0.001
Birth weight, mean (95% CI), g	1,314 (1,252-1,377)	3,611 (3,536-3,685)	< 0.001
Small for gestational age (SGA) at birth, n (%)	10 (6)	7 (5)	1.4 (0.5-3.9)
Male gender, n (%)	88 (57)	87 (57)	1.0 (0.6-1.6)
Surfactant, n (%)	88 (57)	0	NA
Mechanical ventilation, n (%)	91 (59)	0	NA
Postnatal steroids, n (%)	8 (5)	0	NA
Morbidity			
Bronchopulmonary dysplasia (BPD), n (%)	29 (19)	0	NA
Weight < 10 th percentile at discharge, n (%)	85 (55)	NA	NA
Neurodevelopmental impairment (NDI) at 2 years of CA, n (%)	19 (12)	4 (3)	5.2 (0.7-15.7)
Weight < 10 th percentile at 2 years of CA, n (%)	48 (31)	21 (14)	2.8 (1.6-5.0)

CA: corrected age; NA: not applicable.

SGA is defined as weight below the 10th percentile for the gestational age according to the Fenton Intrauterine Growth Curves; BPD is defined as oxygen dependency at 36 weeks' postmenstrual age; NDI is defined as cerebral palsy with the Gross Motor Function Classification System level 2-5, Cognitive and/or Language Composite Scores by Bayley-III -2 SD to -3 SD, and/or moderate or severe hearing and/or visual impairment; weight < 10th percentile at 2 years of CA is defined as weight below the 10th percentile according to the Estonian age- and gender-specific growth standards.

Table 2. Demographic variables of very low gestational age (VLGA; 22⁺⁰ to 31⁺⁶ gestational weeks) and full-term (FT; 37⁺⁰ to 41⁺⁶ gestational weeks) infants.

	VLGA infants (155 infants, 134 mothers)	FT infants (153 infants, 152 mothers)	OR (95% CI) or P-value for comparing means
Maternal age, mean (95% CI), years	31.4 (30.3-32.5)	30.5 (29.7-31.3)	0.194
Maternal higher education, n (%)	36 (27)	76 (50)	0.4 (0.2-0.6)
Paternal age, mean (95% CI), years	34.4 (33.2-35.7)	34.4 (32.2-36.7)	0.210
Paternal higher education, n (%)	20/124 (16)	51/151 (34)	0.4 (0.2-0.7)
Low income of the family, n (%)	31 (23)	18 (12)	2.4 (1.2-4.5)
Number of children in the family, mean (95% CI)	2.2 (2.2-2.4)	1.7 (1.6-1.8)	< 0.001
Age at day care attendance, mean (95% CI), months	22.7 (21.8-23.7)	20.4 (19.6-21.1)	< 0.001
Duration of breastfeeding, mean (95% CI), days	147 (119-175)	308 (273-342)	< 0.001

Higher education is defined as higher professional education or university degree; low income of the family is defined as family's monthly income per one family member < 2,000 Estonian crowns / < 128 EUR.

and Hallermann-Streiff syndrome) and two FT infants had a congenital disease (toxoplasmosis and hypothyreosis) diagnosed after the first week of life. BPD was diagnosed in 29 (19%) of VLGA infants; in 19 (49%) and 10 (9%) of infants born at 22-27 and 28-31 GW, respectively. VLGA infants were more likely to be from low-income families

than FT infants and their parents were less likely to have higher education. During the first year of life 12 (8%) and during the second year 7 (5%) VLGA infants were given a monthly injection of respiratory syncytial virus monoclonal antibody during peak respiratory syncytial virus season. The mean duration of breastfeeding in VLGA infants was significantly

shorter than in FT infants. Most infants were cared for at home in both groups. Only one infant in each group went to day care before the age of 12 months. At the age of 18 months, 5% of VLGA and 14% of FT infants attended some form of organised day care.

Respiratory infections

The mean annual number of RI was 1.5 during the first and 1.9 during the second year of life in VLGA as well as in FT group. If, however, the VLGA group was divided into those born at 22-27 GW and those at 28-31 GW, significant differences during the first year of life were observed. Namely the mean number of RI episodes per child favoured babies with higher GA (**Tab. 3**). The frequency of annual RI divided into none, 1-3, and > 3 episodes was similar between VLGA and FT group during the first as well as the second year of life.

In the multivariate analysis, no associations were found between any of the investigated risk factors and the occurrence of recurrent RI.

Wheezing

Compared with FT, VLGA infants had more wheezing episodes including RW. Furthermore,

those born at 22-27 GW had more RW than those born at 28-31 GW (**Tab. 3**). The presence of BPD was a significant risk factor for wheezing among VLGA infants. VLGA infants with BPD as compared to those without BPD experienced more frequently wheezing (55% vs. 29%; OR: 3.08; 95% CI: 1.34-7.04) as well as RW (28% vs. 10%; OR: 3.31; 95% CI: 1.22-8.97) whereas there was no significant difference between VLGA infants without BPD compared with FT infants in wheezing and RW (29% vs. 21%; OR: 1.51; 95% CI: 0.87-2.62; and 10% vs. 5%; OR: 2.40; 95% CI: 0.93-6.21, respectively).

In multivariate analysis in the whole study population, maternal higher education was protective against wheezing and male gender as well as the presence of BPD promoted wheezing whereas only BPD was associated with RW (**Tab. 4**). In multivariate analysis of the VLGA group, GA (as a continuous variable) was not associated with wheezing or RW, whereas BPD was a significant risk factor for wheezing (OR: 3.17; 95% CI: 1.36-7.41) as well as for RW (OR: 4.96; 95% CI: 1.46-16.83).

Hospitalisation

During the study there were altogether 149 hospital admissions in VLGA and 69 in FT group.

Table 3. Respiratory infections (RI) in very low gestational age (VLGA) and full-term (FT) infants during the first two years of life.

	VLGA infants		OR or IRR* (95% CI)	VLGA infants	FT infants	OR or IRR* (95% CI)
	22-27 GW (n = 39)	28-31 GW (n = 116)		22-31 GW (n = 155)	37-41 GW (n = 153)	
Frequency of RI						
Mean number of RI (min-max) per child	3.8 (0-12)	3.2 (0-12)	1.08 (0.95-1.23)*	3.4 (0-12)	3.4 (0-16)	1.00 (0.92-1.08)*
• 1 st year of life	2.0 (0-8)	1.3 (0-8)	1.23 (1.00-1.51)*	1.5 (0-8)	1.5 (0-8)	1.01 (0.88-1.15)*
• 2 nd year of life	1.8 (0-7)	1.9 (0-7)	0.98 (0.80-1.22)*	1.9 (0-7)	1.9 (0-8)	0.99 (0.88-1.13)*
Recurrent RI, n (%) of infants	19 (49)	47 (41)	1.39 (0.67-2.89)	66 (43)	62 (41)	1.09 (0.69-1.71)
• 1 st year of life	13 (33)	41 (35)	0.91 (0.42-1.97)	60 (39)	55 (36)	1.13 (0.71-1.79)
• 2 nd year of life	15 (38)	58 (50)	0.63 (0.30-1.31)	73 (47)	70 (46)	1.06 (0.67-1.65)
Wheezing						
Mean number of wheezing episodes (min-max) per child	1.2 (0-4)	0.6 (0-4)	1.35 (1.04-1.75)*	0.8 (0-4)	0.4 (0-4)	1.42 (1.13-1.78)*
Wheezing, n (%) of infants	18 (46)	34 (29)	2.07 (0.98-4.36)	52 (34)	32 (21)	1.91 (1.14-3.19)
Recurrent wheezing, n (%) of infants	10 (26)	11 (9)	3.29 (1.27-8.51)	21 (14)	7 (5)	3.27 (1.35-7.14)

*Associations are presented as incidence rate ratios (IRR).

GW: gestational weeks.

Recurrent RI is defined as the presence of a higher number of RI episodes than the population's mean value; recurrent wheezing is defined as ≥ 3 wheezing episodes during the study period.

The overall hospitalisation rate and that due to RI was significantly greater in VLGA than FT infants (**Tab. 5**). However, the proportion of hospital admissions due to RI among all hospitalisations was similar in both groups (53% vs. 57%). Of all RI episodes, 15% in VLGA and 8% in FT infants ($p < 0.001$) were admitted to hospital.

The reasons for hospitalisation due to RI differed between VLGA and FT infants with higher frequency

of bronchitis or bronchiolitis in VLGA infants (**Tab. 5**). No differences between those born at 22-27 GW and 28-31 GW were observed. Among VLGA infants, hospitalisation rate was greater in those with BPD compared to those without BPD (55% vs. 28%; OR: 3.20; 95% CI: 1.40-7.33) whereas hospitalisation rate was also greater in VLGA infants without BPD compared with FT infants (28% vs. 18%; OR: 1.79; 95% CI: 1.02-3.17).

Table 4. Results of the uni- and multivariate analyses of significant risk factors associated with wheezing and hospitalisation during acute respiratory infections during the first two years of life in the whole study cohort of very low gestational age and full-term infants.

	At least 1 wheezing episode		Recurrent wheezing (≥ 3 episodes)		Hospitalisation	
	OR (95% CI) (Univariate analysis)	OR (95% CI) (Multivariate analysis)	OR (95% CI) (Univariate analysis)	OR (95% CI) (Multivariate analysis)	OR (95% CI) (Univariate analysis)	OR (95% CI) (Multivariate analysis)
Maternal higher education	0.45 (0.26-0.78)	0.49 (0.28-0.87)	NS	NS	NS	NS
Male gender	1.90 (1.12-3.21)	1.84 (1.07-3.18)	NS	NS	1.88 (1.10-3.23)	1.82 (1.04-3.18)
Prematurity	1.91 (1.14-3.19)	1.37 (0.78-2.41)	3.27 (1.35-7.94)	2.40 (0.93-6.21)	2.29 (1.34-3.90)	2.99 (1.29-6.92)
Bronchopulmonary dysplasia	3.82 (1.75-8.34)	2.90 (1.24-6.75)	4.93 (1.94-12.54)	3.31 (1.22-8.97)	4.31 (1.97-9.44)	1.84 (1.04-3.27)

NS: not significant.

Higher education is defined as higher professional education or university degree; bronchopulmonary dysplasia is defined as oxygen dependency at 36 weeks' postmenstrual age.

Table 5. Hospitalisation and antibiotic consumption in very low gestational age (VLGA) and full-term (FT) infants during the first two years of life.

	VLGA infants		OR (95% CI) or P-value for comparing means	VLGA infants	FT infants	OR (95% CI) or P-value for comparing means
	22-27 GW (n = 39)	28-31 GW (n = 116)		22-31 GW (n = 155)	37-41 GW (n = 153)	
Hospitalisation						
All hospitalisations, n (%) of infants	23 (59)	62 (53)	1.25 (0.60-2.61)	85 (55)	47 (31)	2.74 (1.72-4.37)
Hospitalisations due to RI, n (%) of infants	15 (38)	36 (31)	1.39 (0.65-2.96)	51 (33)	27 (18)	2.29 (1.34-3.90)
Reason of hospitalisation due to RI						
• URTI, n (%) of hospitalisations	4 (17)	18 (33)		22 (28)	18 (46)	
• Bronchitis/bronchiolitis, n (%) of hospitalisations	16 (67)	25 (45)	0.176	41 (52)	11 (28)	0.040
• Pneumonia, n (%) of hospitalisations	1 (4)	8 (15)		9 (11)	3 (8)	
• Otitis, n (%) of hospitalisations	3 (13)	4 (7)		7 (9)	7 (18)	
Antibiotics						
Antibiotic consumption during RI, n (%) of infants with RI	29/37 (78)	70/99 (71)	1.50 (0.61-3.67)	99/136 (73)	75/134 (56)	2.10 (1.27-3.50)
• 1 st year of life	17/30 (57)	32/68 (47)	1.47 (0.62-3.49)	49/98 (50)	39/104 (38)	1.67 (0.95-2.92)
• 2 nd year of life	25/32 (78)	55/86 (64)	2.01 (0.78-5.19)	80/118 (68)	64/119 (54)	1.81 (1.07-3.07)

GW: gestational weeks; RI: respiratory infections; URTI: upper respiratory tract infections.

Male gender, prematurity, and BPD were independent risk factors for hospitalisation in the multivariate analysis in the whole study population (**Tab. 4**). In multivariate analysis of the VLGA group, GA (as a continuous variable) was not associated with hospitalisations due to RI whereas BPD appeared to be a significant risk factor (OR: 3.20; 95% CI: 1.40-7.33).

Antibiotic consumption

The odds of receiving antibiotics due to RI were 2.1 times greater for VLGA as compared with FT infants (**Tab. 5**). Again, VLGA infants with BPD received antibiotics more often than those without BPD (83% vs. 60%; OR: 3.26; 95% CI: 1.17-9.12) whereas there was no significant difference in VLGA infants without BPD compared with FT infants (60% vs. 49%; OR: 1.53; 95% CI: 0.95-2.46).

Discussion

In the present population-based study covering the entire annual birth cohort of Estonia we observed a similar frequency of RI among VLGA and FT infants during the first two years of life. On closer examination, however, a greater frequency of RI among those born at 22-27 GW as compared with the other GA categories was observed in the first year of life. Despite the similar rate of RI in both groups, VLGA infants experienced more wheezing and RW episodes, especially those born before 28 GW. Moreover, VLGA infants also required hospitalisations and received antibiotics due to RI more frequently. However, there was no significant difference between VLGA infants without BPD compared with FT infants in wheezing and RW. In multivariate analyses it was not prematurity in itself but the presence of BPD that appeared to be the most important independent risk factor for unfavourable outcomes of RI.

The main strengths of this nationwide cohort study are the inclusion of the entire annual cohort of very preterm births in Estonia and having an age, gender, and geographic location matched control group of FT infants. The use of GA instead of birth weight as an inclusion criterion reduced the proportion of infants who were small for their GA at birth. The attainment of very high follow-up rates close to 100% should also be noted.

In the present study, we describe a lower mean annual number of RI for VLGA infants as well as for FT infants than reported in Germany (1.5 vs. 3.1

RI episodes in the first and 1.9 vs. 3.2 episodes in the second year of life, respectively) and in the United States (5.1 episodes per child-year during the first three years of life) [1, 2]. Late day care attendance due to 18 months of fully paid parental leave in Estonia is one of the most obvious contributing factors. Attendance of day care has been identified as a significant risk factor for RI in several studies regardless of the day care setting, size of the day care group, or the number of hours spent in day care [1, 19]. In our study the mean age of day care entry was 22.7 months in VLGA and 20.4 months in FT infants and only one child in both groups attended day care at the age of 12 months. In a study performed in the Netherlands, 66% of 12-month-old children attended day care [20]. Another factor in the low rate of RI that should be noted is the retrospective design of parental interviews which potentially may miss some mild cases of RI and thus lead to the under-reporting of RI.

Depending on the country, study design, and year, at least one episode of wheezing has been described in 15-39% of children [13, 21] during the first years of life with the occurrence of RW in 12-36% of children [21]. In addition, wheezing and RW are more common in premature as compared with FT infants, occurring in up to 40-68% and 13-25%, respectively [12, 22, 23]. Similarly, higher prevalence of wheeze and RW was observed in our study among VLGA infants as compared with FT infants (34% vs. 21% and 14% vs. 5%, respectively). However, we should emphasize that the prevalence of both was in the lower end of the previously reported data in other countries [12, 13, 21-23]. We suggest that a relatively low rate of RI could be just one reason. Although important gaps remain in the current knowledge regarding the role of viral RI in infancy in the inception of asthma [24], wheezing and prematurity have been associated with respiratory morbidity in future life [25]. Whether a relatively low frequency of RI and wheezing episodes in our study cohort might predict better long-term respiratory health, it needs further long term studies.

Despite the similar frequencies of RI, the hospitalisation rates were significantly higher in VLGA, suggesting at least in part a more severe disease in VLGA than FT infants. Significant country-wide differences reported in hospitalisation rates might reflect variations in patient management with different thresholds for hospitalisation. In terms of VLGA infants, our hospitalisation rates were well in line with those in other countries. In the first two years of life 33% of VLGA, 55% of the ones with BPD and 28% of the ones without,

and 18% of FT infants were admitted to hospital due to RI at least once in Estonia. In a French study of infants born prior to 29 weeks of gestation, 47% were readmitted at least once within the first 9 months of life and the re-hospitalisation rate was twice as high for children who had had chronic lung disease [26]. Similarly, in a US study [27] in the cohort of infants born before 33 GW, 49% of infants with BPD were re-hospitalised in the first year of life, more than twice the rate of re-hospitalisation of the non-BPD population, which was 23%. However, much lower rates of hospitalisations have been reported for preterm as well as for FT infants in Switzerland: 25% of preterm infants with median GA of 28.7 weeks and only 1.5% of infants born at term had to be hospitalised for respiratory problems in their first year of life [12, 13].

Routine antibiotic use for viral RI is not recommended in evidence-based clinical practice guidelines [28]. Nevertheless, despite the rarity of serious bacterial infections, antibiotics are frequently used in children younger than 24 months [29]. In the present study we noted that antibiotic consumption during RI was relatively high, especially in VLGA infants. These findings likely reflect the cautious approach of paediatricians and family doctors in treating RI during the first years of life. On the other hand, diagnostic limitations and lack of rapid tests for distinguishing between bacterial and viral RI may also play a role, at least in the initiation of empiric therapy.

A vast number of risk factors (e.g. abnormal early lung function including BPD, day care attendance, male gender, parental smoking, family size, exposure to home dampness and mould, and prematurity) have been associated with recurrent RI, wheezing, and hospitalisations due to RI in the first years of life [1, 3, 12, 13, 20-22, 30]. Although the protective role of breastfeeding and maternal university education against recurrent RI and infant wheezing is well known in developing countries, the effect in more developed countries is less clear [3, 21]. In the present study four risk factors – low maternal education, male gender, prematurity, and the presence of BPD – were found to be significant for unfavourable outcomes of RI (wheezing, RW, and hospitalisation) whereas BPD was the only one for all of them.

The present study was carried out in a relatively unique socio-demographic setting characterised by late day care attendance and small family size. Nevertheless, from a clinical point of view our results suggest a tailored approach when planning hospital discharge of VLGA infants. Special

attention should be targeted to the parents of infants born before 28 GW or with BPD in counselling to limit the exposure of their children to respiratory viruses and environmental risk factors. Additionally, national immunisation programmes for preterm babies should be adapted accordingly, particularly in the countries with limited resources.

The retrospective design of parental interviews should be noted as a main limitation of the study. While all RI cases treated at home were identified only by parental reports, there exists a possibility of a memory bias which we believe is similar in parents of VLGA and FT infants. Still it may lead to underreporting of mild RIs. Secondly, data about relevant childhood immunisations and common environmental risk factors, like parental smoking and presence of pets at home, were not collected. According to the national statistics by the age of 2 years up to 95% of children in Estonia have received all immunisations recommended by the national programme [31]. Thus we believe that abovementioned limitations did not preclude us from drawing adequate conclusions.

Conclusions

The frequency of RI in general was similar among VLGA and FT infants, except for those born at 22 to 27 GW. Nevertheless, VLGA infants had more wheezing episodes and hospitalisations due to RI than their FT counterparts. However, there was no significant difference between VLGA infants without BPD compared with FT infants in wheezing and RW. BPD was the main risk factor for all unfavourable outcomes of RI among VLGA infants. These data suggest that still in the era of modern perinatal care BPD is more likely than prematurity in itself to predispose VLGA infants to a more severe clinical course of RI. Consequently, the study emphasizes the need to allocate resources for prevention of RI, first of all, to VLGA infants with BPD and to those born before 28 GW. Overall, efforts to reduce BPD and a better knowledge of the peri- and postnatal factors that affect immature lungs should be a key priority for health care while striving to decrease long-term respiratory sequelae and the costs of acute respiratory morbidity of VLGA infants.

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