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Very low gestational age infants in Estonia

Measuring outcomes and insights into prognostic factors

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UNIVERSITY OF TARTU
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Department of Paediatrics, University of Tartu, Tartu, Estonia

Dissertation was accepted for the commencement of the degree of Doctor of Philosophy in Medicine on 27th of August 2014 by the Council of the Faculty of Medicine, University of Tartu, Estonia

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Commencement: 29th of October 2014

Publication of this dissertation is granted by the University of Tartu.

The research was supported by the European Union through the European Social Fund.

ISSN 1024-395X
ISBN 978-9949-32-671-6 (print)
ISBN 978-9949-32-672-3 (pdf)

University of Tartu Press
www.tyk.ee

To my family
for sharing our life
with very preterm babies

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I Toome L, Varendi H, Andresson P, Ilmoja ML, Kallas E, Maipuu L, Saik P, Kool P, Ormisson A. Väga enneaegsete vastsündinute ravitulem Eestis. *Eesti Arst* 2009;88(Lisa 4):12−20.

II Toome L, Ringmets I, Andresson P, Ilmoja ML, Saik P, Varendi H. Changes in care and short-term outcome for very preterm infants in Estonia. *Acta Paediatr* 2012;01(4):390−6.

III Toome L, Varendi H, Männamaa M, Vals MA, Tänavsuu T, Kolk A. Follow-up study of 2-year-olds born at very low gestational age in Estonia. *Acta Paediatr* 2013;102(3):300–7.

IV Toome L, Plado S, Ringmets I, Vals MA, Varendi H, Lutsar I. Respiratory infections in very low gestational age infants: a population-based cohort study in Estonia. *J Pediatr Neonat Individual Med* 2014;3(1):e030115.

Degree of the applicant's personal contribution to the publications:

In all publications Liis Toome participated in study design, data collection, analysis, and interpretation of data from studies. She drafted all manuscripts and was responsible for the responses and updates throughout the review process.

2. ABBREVIATIONS

BPD	bronchopulmonary dysplasia
BSID	Bayley Scales of Infant Development
BW	birth weight
CA	corrected age
CI	confidence interval
CP	cerebral palsy
CPAP	continuous positive airway pressure
ELBW	extremely low birth weight
ELGA	extremely low gestational age
EPT	extremely preterm
FT	full-term
GA	gestational age
GMFCS	Gross Motor Function Classification System
GW	gestational week(s)
IQ	intelligence quotient
IQR	interquartile range
IRR	incidence rate ratio
MDI	Mental Developmental Index
MV	mechanical ventilation
NDI	neurodevelopmental impairment
NEC	necrotising enterocolitis
NICU	neonatal intensive care unit
OR	odds ratio
PDI	Psychomotor Developmental Index
PDA	patent ductus arteriosus
PIVH	peri/intraventricular haemorrhage
PMA	postmenstrual age
PPROM	preterm premature rupture of the membranes
PSOM	Paediatric Stroke Outcome Measure
PVL	periventricular leucomalacia
QALY	quality-adjusted life years
RDS	respiratory distress syndrome
RI	respiratory infection(s)
ROP	retinopathy of prematurity
RW	recurrent wheezing
SD	standard deviation
SGA	small for gestational age
VLBW	very low birth weight
VLGA	very low gestational age
VPT	very preterm

3. INTRODUCTION

Advances in perinatal care have improved the survival of very preterm (VPT; born at <32 completed gestational weeks (GW) and/or with birth weight (BW) <1500 g) infants dramatically (Fanaroff et al. 2003). However, survival and later neurological and developmental outcomes for these infants, especially for extremely preterm (EPT, born at <28 GW and/or BW <1000 g) infants, remain of concern because of significant mortality and morbidity rates. About 1 to 1.5% of all births is at <32 GW, but these infants account for one third to one half of all neonatal and infant deaths (EURO-PERISTAT Project 2010). Additionally they remain at substantial risk for a wide spectrum of long-term morbidities (Saigal and Doyle 2008), which leads to high emotional and economic costs for their families (van der Pal et al. 2007) and for society (Phibbs and Schmitt 2006, Korvenranta et al. 2010).

Providing quality care is a core principal of modern healthcare. Advances in perinatal care of VPT infants have resulted in improvements in gestation-specific survival rates such that, in the developed countries as well as in Estonia, mortality is no longer a particularly useful measurement of quality of care. If the aim of neonatal care is to achieve long-term survival free of handicap, then it is mandatory that any assessment of the quality of care for VPT infants must include the long-term outcome for these infants. It is important to document the long-term outcomes of survivors of VPT births and to link this to events within the perinatal period. In general, 2 years corrected for gestational age (GA) at birth is considered an acceptable time for collecting initial follow-up data about VPT infants. At this age, it is likely that the findings will still be relevant to current clinical practice, and the effects of social and demographic factors are minimised (Lyon 2007). Healthcare and health-system factors also play a role in outcome for VPT infants more generally. For VPT births, delivery in a tertiary level maternity unit with an onsite tertiary level neonatal intensive care is associated with lower mortality (Poets et al. 2004, Marlow et al. 2014). It has also been shown that long-term health outcomes for EPT infants are better if they receive their whole initial neonatal care in tertiary level units (Rautava et al. 2013).

Population-based study designs and standardised data collection have been recommended for the evaluation of perinatal care services, as well as for studies of prognosis (Evans and Levene 2001, Marlow 2003). Since the introduction of antenatal steroids and postnatal surfactant therapy in perinatal treatment of VPT infants, studies from developed countries have presented population-based as well as nationwide short-term and long-term outcomes for VPT and EPT infants. However, although some data are available, no nationwide studies have been published that relate to Eastern European countries, which have more limited resources and less experience in the care of EPT infants than the developed countries.

In Estonia, the only previously published data with respect to the outcome of VPT infants are for infants with a BW less than 1500 g born in 1999–2000 at the infants' age of 3 years (Ormisson et al. 2009). Therefore, the studies of the present thesis were undertaken with the primary objectives to, first, describe the short-term and long-term outcome for VPT infants in Estonia after introduction of modern perinatal and neonatal care, and second, to benchmark altogether the quality of healthcare services for these vulnerable infants in Estonia and to identify key areas for ongoing national quality improvement initiatives.

4. REVIEW OF LITERATURE

4.1. Epidemiology of preterm birth

Definitions of preterm birth

In humans, gestational length to non-elective delivery has been estimated at 282–283 days (Bergsjo et al. 1990). Preterm birth occurs before 37 completed GW (World Health Organization 1977) and could further be subdivided into moderately preterm, VPT, and EPT (Figure 1). Definitions in the literature vary, but the limit of VPT birth is often set at <32 completed GW, whereas infants born at <28 completed GW are considered EPT. There has been no general agreement on the lower limit for defining preterm infants, or that used to distinguish preterm birth from spontaneous abortion. However, the lower limit at 22 completed GW is used in collecting birth register data and in calculation of perinatal mortality in many countries (Macfarlane et al. 2003), including Estonia.

Preterm birth <37 GW			Term birth 37–41 GW	Postterm birth ≥42 GW
Extremely preterm <28 GW	Very preterm 28–31 GW	Moderately preterm 32–36 GW		

Figure 1. Categorisation of GA by completed GW at birth

In previous research, the definitions of low, very low, and extremely low BW of <2500 g, <1500 g, and <1000 g, respectively, have been widely used as proxys for preterm birth. However, studies defining preterm births solely on BW criteria are limited by some degree of misclassification as growth restricted infants with more advanced GA are probably over represented in such studies. It is thus better practice to define outcome by GA and then to study the effect of foetal growth restriction in these defined populations (Marlow 2004).

To determine GA at birth, it is necessary to date the pregnancy and calculate the expected date of delivery, most commonly as 280 days from the first day of the last menstrual period. Despite problems of recalling the correct date of the last menstrual period, the estimations of GA are reasonably good (Savitz et al. 2002) and can be used in perinatal epidemiology research when other dating methods are unavailable. A more accurate way to date the pregnancy is to measure foetal size in early pregnancy, within the first trimester, using ultrasound techniques (Kramer et al. 1988). Importantly, changing the pregnancy dating method from last menstrual period to ultrasound could have an impact on GA distribution, leading to an increase in preterm birth rate (Goldenberg et al. 1989). Hence, rates of preterm birth may not be comparable if these are based on different methods of

estimating GA; publications reporting foetal and neonatal outcomes should clearly describe methods used to determine GA (Engle 2004).

In the following text, infants born with a GA of <32 weeks or a BW of <1500 g are referred to as very low gestational age (VLGA) or very low birth weight (VLBW) infants, whereas infants born with a GA of <28 weeks or a BW of <1000 g are referred to as extremely low gestational age (ELGA) or extremely low birth weight (ELBW) infants. In general, VLGA and VLBW infants are taken together as VPT infants and ELGA and ELBW infants as EPT infants.

Age terminology during the perinatal period

Standardised terminology should be used when defining ages and comparing outcomes of foetuses and VPT infants. The recommended terms by American Academy of Paediatrics (Engle 2004) are (Figure 2):

- GA (completed weeks): time elapsed between the first day of the last menstrual period and the day of delivery. If pregnancy was achieved using assisted reproductive technology, GA is calculated by adding 2 weeks to the conceptional age.
- Chronological age (days, weeks, months, or years): time elapsed from birth.
- Postmenstrual age (PMA) (weeks): GA plus chronological age.
- Corrected age (CA) (weeks, months, or years): chronological age reduced by the number of weeks the infant was born before 40 GW; the term should be used only for children up to 3 years of age who were born VPT.

During the perinatal period and neonatal hospital stay, PMA is preferred to describe the age of preterm infants. After the perinatal period, CA is the recommended term.

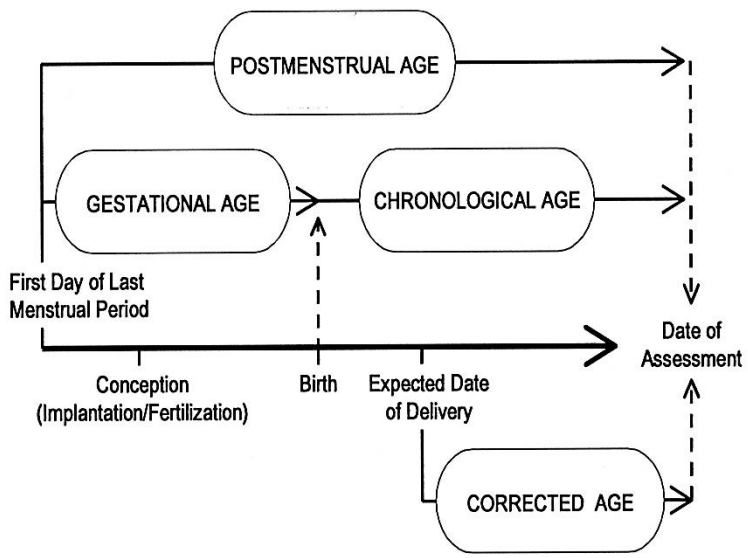


Figure 2. Age terminology during the perinatal period (Engle 2004)

Rates of preterm births

In 2010, an estimated 14.9 million babies (uncertainty range 12.3–18.1 million) were born preterm, 11.1% of all live births worldwide (Blencowe et al. 2012).

In Estonia, the prevalence of preterm births was the highest at 6.6% in 1992 and the lowest at 5.3% in 2010 (National Institute for Health Development 2014). This is low in comparison with the international prevalence of preterm births in developed countries; a preterm birth rate of 12.7% has been reported in the United States of America (Heron et al. 2010) and the prevalence ranges from 5 to 10% in Europe (EURO-PERISTAT Project 2010). In developing countries, rates are even higher. A study from Malawi reported that 20% of women delivered preterm (van den Broek et al. 2005).

Blencowe et al. has estimated time trends for preterm birth rates for 65 countries in the developed world, Latin America, and the Caribbean regions. Only three countries, one of them Estonia, had reductions in estimated preterm birth rates from 1990 to 2010 (Blencowe et al. 2012). Rates of preterm birth were stable in 14 countries and increased in 48 countries. Much of the increase in the singleton preterm birth rate is explained by rising numbers of indicated preterm births. A high number of multiple gestations associated with assisted reproductive technologies are also an important contributor to the overall increase in preterm births whereas singleton pregnancies after in-vitro fertilisation are also at increased risk of preterm birth (Jackson et al. 2004).

From 1992 to 2011, the rate of VLGA births in Estonia stayed between 1.0 and 1.3% (National Institute for Health Development 2014). This compares favourably to the rate of VLGA births in other parts of Europe, which varies from 0.7% in Iceland to 1.7% in the Northern United Kingdom (Field et al. 2009, EURO-PERISTAT Project 2010). The prevalence of VLBW births in the United States of America stands at 1.6% (Mathews and MacDorman 2008).

Risk factors for preterm birth

The obstetric precursors leading to preterm birth are: 1) delivery for maternal or foetal indications, in which labour is either induced or the infant is delivered by pre-labour (elective) caesarean section; 2) spontaneous preterm labour with intact membranes; and 3) preterm premature rupture of the membranes (PPROM), irrespective of whether delivery is vaginal or by caesarean section (Goldenberg et al. 2008).

Common reasons for indicated preterm births include pre-eclampsia or eclampsia, and intrauterine growth restriction (Goldenberg et al. 2008). Births that follow spontaneous preterm labour and PPROM – together called spontaneous preterm births – are regarded as a syndrome resulting from multiple causes, including infection or inflammation, uteroplacental ischaemia or haemorrhage, uterine over distension, stress, and other immunologically mediated processes (Romero et al. 2006, Romero et al. 2014). The precursors vary by GA (Mueller-Heubach et al. 1990, Steer 2005), with the precise cause of spontaneous preterm labour being unidentified in up to half of all cases (Menon 2008). There are many maternal and foetal characteristics that have been associated

with preterm birth, including maternal demographic characteristics (young or advanced age, black race, low socioeconomic and educational status, single marital status, absence of health insurance), nutritional status (low body-mass index), pregnancy history (a previous preterm birth, short inter-pregnancy intervals), present pregnancy characteristics (multiple pregnancy, vaginal bleeding caused by placental abruption or placenta praevia, cervical insufficiency, extremes of the volume of amniotic fluid), psychological characteristics (clinical depression during pregnancy), and adverse behaviours (smoking, heavy alcohol consumption) (Goldenberg et al. 2008). Family history of preterm birth is a strong risk factor as well (Plunkett and Muglia 2008). Maternal medical disorders, such as thyroid disease, asthma, diabetes, and hypertension, are associated with increased rates of preterm delivery, many of which are indicated because of maternal complications (Goldenberg et al. 2008). However, there is abundant evidence that infection and the inflammation generated by infection, whether within the gestational tissues or elsewhere, are a primary cause of a substantial proportion of preterm births (Goldenberg et al. 2000, Agrawal and Hirsch 2012). The mechanisms by which intrauterine infections lead to preterm labour are related to activation of the innate immune system (Romero et al. 2006, Agrawal and Hirsch 2012, Ferguson 2014).

Nowadays, it is recognised increasingly that previous understanding of preterm delivery has been limited by the failure to accept the idea that preterm birth is a syndrome with a number of etiologic factors and phenotypic characteristics, many of which are independent of each other (Villar et al. 2012, Romero 2014). Therefore, Villar and his colleagues propose a classification that is based on clinical phenotypes that are defined by ≥1 characteristics of the mother, the foetus, the placenta, the signs of parturition, and the pathway to delivery (Villar et al. 2012). They describe five components in a preterm birth phenotype: 1) maternal conditions that are present before presentation for delivery; 2) foetal conditions that are present before presentation for delivery; 3) placental pathologic conditions; 4) signs of the initiation of parturition; and 5) the pathway to delivery.

Previously social variations in low BW and preterm birth have been studied in Estonia. The birth-register studies from the 1990s showed that maternal age <20 years (Haldre et al. 2007) and low education as well as marital status (single mother) and nationality (non-Estonians) were all independently related to the risk of preterm birth (Koupilova et al. 2000). However, a recent study of time trends of socio-demographic determinants of preterm birth in Estonia during 1992–2010 (Varendi 2012) showed that since the re-establishment of the Estonian Republic in 1991, the proportion of preterm birth has decreased among parents at the age above 30 years, with primary or basic education, and of non-Estonian nationality. Single status remained a risk factor for preterm delivery, as unregistered cohabiting and rural living had lost their importance (Figure 3).

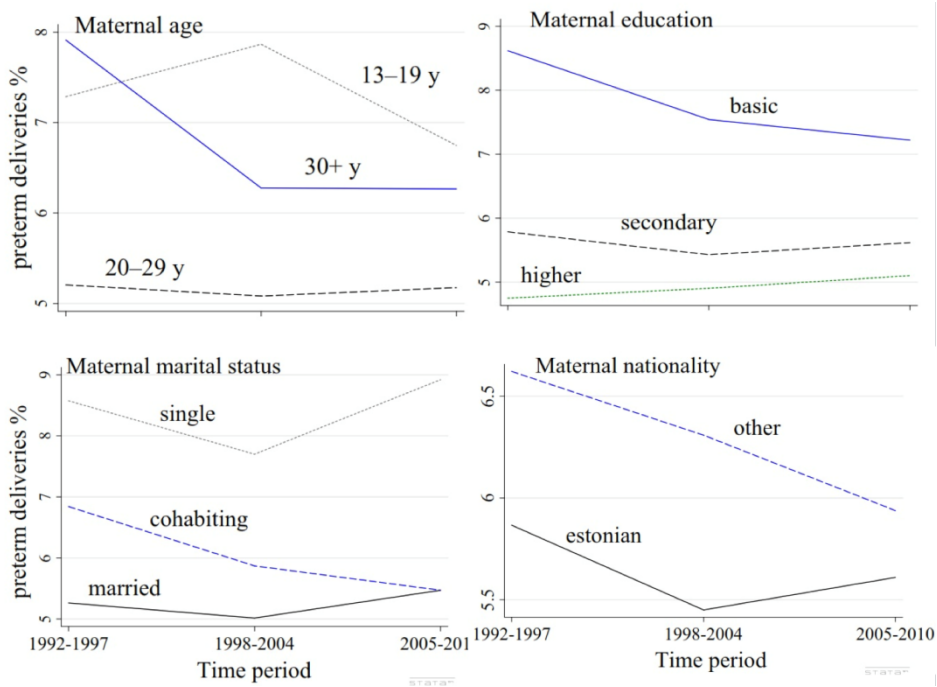


Figure 3. Trends of preterm deliveries among maternal socio-demographic determinants in Estonia (Varendi 2012)

4.2. The changing face of intensive care for preterm infants

Neonatal care before 1965

Ironically, the history of neonatology began with innovative French midwives and obstetricians, not with paediatricians. Parisian obstetrician Stephane Tarnier modified a warming chamber for the rearing of poultry to develop the Tarnier-Martin Couveuse in 1878, an isolette that decreased the neonatal death rate to 38 from 66% for infants with BW less than 2000 g. Nevertheless, it was not until the 1950s and 1960s that premature baby units became established in a number of large hospitals emphasising the importance of 24-hour nursing care. Along with the establishment of autopsy services, it became apparent that the principal causes of death were immaturity, respiratory distress with histological evidence of hyaline membrane disease in the lungs, and intracranial haemorrhage (Wyatt 2010). Until the end-1950s, the primary support for respiratory distress was the provision of high inspired oxygen concentrations. Consequently, many preterm infants developed retrolental fibroplasia, now called retinopathy of prematurity (ROP), a disease virtually unknown before 1940s, but in the early 1950s it had become the leading cause of blindness in children in the United States of America (Philip 2005).

1965 to 1985

The 1960s are considered to be the start of current modern practise of neonatal medicine, and the time when the premature nursery became a neonatal intensive care unit (NICU). Development of techniques to measure arterial blood gas levels and the development of intermittent positive pressure ventilation in preterm infants contributed to the more accurate assessment and aggressive management of respiratory disorders (Wyatt 2010). It was determined that the term respiratory distress syndrome (RDS) was more appropriate than hyaline membrane disease, as the last was a pathologic diagnosis. Because of the uncertain cause, "idiopathic" was frequently placed before RDS. Chronic lung disease, bronchopulmonary dysplasia (BPD), first described by Northway (Northway et al. 1967), was increasingly recognised in survivors who had received mechanical ventilation (MV), leading to many weeks or months of oxygen dependency and hospital care. The use of continuous positive airway pressure (CPAP) to prevent alveolar collapse was introduced in the United States of America in the 1970s (Gregory et al. 1971) and nasal CPAP has grown in importance as a mean of providing minimally invasive respiratory support.

Peri/intraventricular haemorrhage (PIVH) was known to be a common autopsy finding in VPT babies who died in the first days of life, but it was thought to be a catastrophic event. However, in the late 1970s it became possible to image the infant brain during life, with the introduction of computed tomography, and since the 1980s, with real-time cranial ultrasound (Wyatt 2010). It became apparent that there was a disturbingly high incidence of PIVH in VLBW survivors and numerous follow-up studies were started worldwide to relate cranial ultrasound findings in the neonatal period with long-term neurological and developmental outcomes (Stewart et al. 1987). Real-time ultrasound scanning made it also possible to document the evolution of periventricular leucomalacia (PVL), an ischemic lesion in periventricular white matter, and thus to define the clinical neurological correlates in the neonatal period (Dolfin et al. 1984).

A concept of regionalisation was introduced and methods for transporting sick infants by ambulances were being established. The comparative data indicated that mortality and morbidity were higher in infants who had been transferred to centres postnatally in comparison with those who had been born at the centre (Usher 1971). When mothers were transferred to the centre to deliver, the data showed that such maternal-foetal transfers had mortality and morbidity that was similar to those who originally planned to deliver at the centre (Philip et al. 1981).

1985 to 1995

The first successful use of exogenous surfactant for the treatment of RDS was described in Japan (Fujiwara et al. 1980), but there was a long delay before the findings were translated into a widely accepted clinical therapy. Similarly, although antenatal steroids in preterm labour were first shown to be effective in reducing the severity of RDS in 1972 (Liggins and Howie 1972), there was a

remarkable delay before the use of antenatal steroids became universally accepted. By the early 1990s, there was overwhelming evidence that the combination of antenatal steroids and surfactant after birth led to a dramatic reduction in the severity of RDS and its consequences. However, this period was also characterised by increasing use of the artificial corticosteroid dexamethasone for treatment of BPD. It was shown in a randomised trial that in preterm infants who were ventilator dependent, a prolonged course of high-dose dexamethasone led to faster weaning from ventilator compared with control infants (Cummings et al. 1989). Following this study dexamethasone was increasingly adopted by neonatologists across the world and little concern was expressed at the time about the body of experimental data showing that prolonged courses of high-dose postnatal steroids could have detrimental effects on the developing brain (Yeh et al. 1997, Yeh et al. 1998).

1995 to present

The 1990s has been the decade of the micro-preemie. Successful treatment of infants, with GA of 23 to 25 weeks and BW of 500 to 750 g, has been possible through surfactant therapy, more proactive obstetric management, precision micromanagement of fluid delivery, sophisticated nutritional management, and continued improvement in ventilator management (Wyatt 2010). Awareness of early management in the delivery room during the first 60 minutes after birth with the beneficial use of prophylactic surfactant and institution of early CPAP and it′s effect on long-term outcome increased (Lussky 1999). In the modern era, prolonged MV is often not required and many ELGA infants may be supported with CPAP from the first days of life. This has meant that the severe and damaging fluctuations in oxygen, carbon oxide, blood pressure, and other physiological variables are avoided. The frequent episodes of cardio-respiratory collapse and recovery, which were a feature of care in the 1970s and 1980s, are now mercifully unusual (Wyatt 2010). In addition, nowadays is widely used the Newborn Individualised Developmental Care and Assessment Programme introduced by Heidelise Als, which support family-centered, individualised developmental care for premature infants while shortening ventilator days and improving developmental outcomes of NICU graduates (Als and Gilkerson 1997). Also, some strategies that have improved long-term outcomes, such as caffeine therapy for apnoea of prematurity (Schmidt et al. 2007), have appeared in the 2000s.

Unfortunately, BPD and necrotising enterocolitis (NEC) have remained significant clinical problems and there is evidence to suggest that infection may have become an increasing problem over the last decade. Antenatal infection is increasingly recognised both as an important cause of preterm labour and as a causal mechanism underlying a significant proportion of perinatal brain injury. Furthermore, impaired growth of both body and head is common over the first weeks of life and the problem is exacerbated by frequent episodes of sepsis, leading to interruption in enteral and parenteral feeding (Wyatt 2010). Additio-

nally, there is no consensus in the management of patent ductus arteriosus (PDA) (Benitz 2010).

In general, during all of the abovementioned periods, the changes in the perinatal and neonatal care have been followed by controversy about the wisdom of providing intensive care for babies born at the limit of viability for that period of time. It seems unlikely that the current limits of viability at 22–23 GW will change within the next decades. The goal of the current neonatal care is to ensure that infants who can benefit from conventional methods of intensive care have the best possible chance of intact survival with normal brain development.

4.3. Short-term consequences of very preterm birth to the individual

4.3.1 Mortality

The outcome of VPT infants born 50 years ago was poor. Of the VLBW infants admitted to the Colorado General Hospital Premature Infant Centre, only 50% survived the first year of life (Lubchenco et al. 1963). Changes in perinatal management, including increased antenatal referral, antenatal steroid treatment, assisted respiratory support at delivery, and surfactant therapy, have been associated with a substantial increase in survival of infants at low GA (Fanaroff et al. 2003). Nevertheless, these infants account for one third to one half of all perinatal, neonatal, and infant deaths (EURO-PERISTAT Project 2010). Although the perinatal mortality rate of VLGA infants has decreased dramatically in Estonia since 1992 (Figure 4), 49% of all perinatal deaths in Estonia in 2011 occurred in infants born below 1500 g of BW (National Institute for Health Development 2014). Similarly, Callaghan et al. have shown that 34% of all infants dying in the United States of America are VLGA/VLBW infants (Callaghan et al. 2006).

Calculations of mortality up to the first discharge of live-born EPT/VPT infants and/or of EPT/VPT infants admitted to intensive care as denominators are most often used. The Neonatal Research Network of the National Institute of Child Health and Human Development reported a decline in VLBW infant mortality from 26% in 1988 to 16% in 1995–1996 (Hack et al. 1991b, Lemons et al. 2001). Similarly, Horbar et al. demonstrated an improvement in the mortality rates from 18 to 15% over the years 1991–1999 for infants who weighed 500 to 1499 g, but his data did not show any significant change in mortality over the last few years of the study, 1997–1999 (Horbar et al. 2002). In an another study, mortality rates for VLBW infants were similar to previously published data for the years 1997–1999 and did not change over time thereafter until 2004 (Mohamed et al. 2010). Altogether, it seems that a decline in mortality that occurred in the last two decades of the 20th century reached a plateau by the end of 1990s. Whether this was attributable to the aggressive resuscitation of nonviable infants resulting in a delay in their time of death is not yet clear.

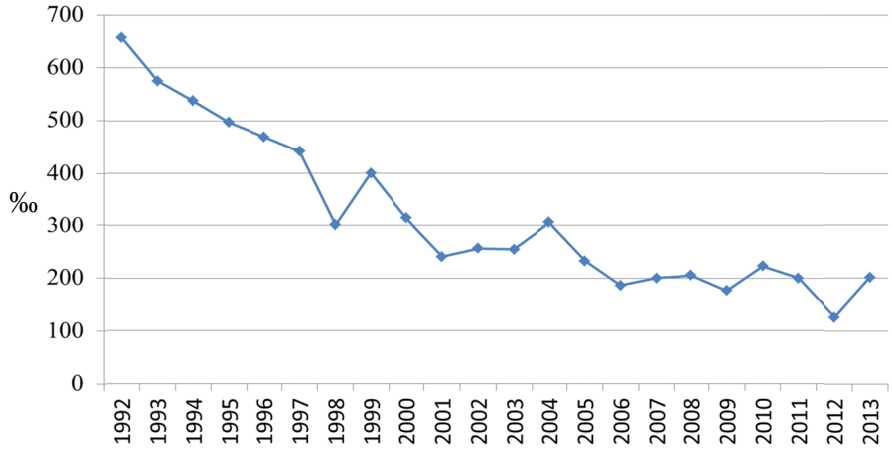


Figure 4. Perinatal mortality rate per 1,000 births of VLGA infants in Estonia (National Institute for Health Development 2014)

Data on survival often come from specialised neonatal units, with a selection bias resulting from different criteria for referral, admission, or treatment. This partly explains the better survival rates, especially for the lowest GA, observed in some single or multiple centre networks than in population-based studies (Evans and Levene 2001). Additionally, mortality risks are inversely related to GA. In the population-based studies done since the nineties, the survival for ELGA/ELBW infants ranges from 39 to 81% in Europe (Costeloe et al. 2000, Vanhaesebrouck et al. 2004, Markestad et al. 2005, Tommiska et al. 2007, EXPRESS group 2010, de Waal et al. 2012) and for VLGA/VLBW infants from 81 to 88% (Zeitlin et al. 2010, Rüegger et al. 2012). A study of 10 European regions in 2003 presented the survival rate in VPT infants as ranging from 79 to 93%, indicating the variability of treatments provided in this population (Zeitlin et al. 2008). The respective figures for VLGA/VLBW infants outside of Europe are 93% in the United States of America (Bode et al. 2009), 90% in Australia (Darlow et al. 2003), and 89% in Japan (Kusuda et al. 2006) whereas for ELBW infants, for example, 83% in Japan (Itabashi et al. 2009).

Babies born at the threshold of viability

Although relatively small in numbers, babies born at or around the limit of viability frequently die because of decisions taken shortly after delivery to limit intensive care and provide only palliative treatment (Larroque et al. 2004). Therefore, they generate a great deal of public interest and a range of often-polarised options.

In recent years, the Nuffield Council for Bioethics (Nuffield Council on Bioethics 2006) has reviewed the evidence surrounding the appropriateness of treatment for such babies and updated professional guidance from the United Kingdom has been published (Wilkinson et al. 2009). In broad terms, these

documents suggest that before 23 GW, intervention is not appropriate; at 23 GW, health professionals should discuss with parents the provision of active intervention given the individual circumstances; while at 24 GW, the broad expectation would be to proceed with active intervention and intensive care unless a baby was in very poor condition at birth. In other countries, such as the Netherlands, current policy follows a non-interventionist stance for babies born at the limits of viability (Dutch Paediatric Association 2011), whereas in contrast, in some parts of the world there appears to be a greater willingness to provide full intensive care to babies at 22 GW (Sugiura et al. 2011).

Seaton et al. assessed the care given to the babies born at the threshold of viability over the last 20 years using regional and national data from the former Trent health region, United Kingdom. The proportion of babies surviving to discharge increased significantly from 1991 to 2010 for those born at 24 and 25 GW but failed to achieve statistical significance for those at 23 GW. No babies born at 22 GW survived (Seaton et al. 2013). The results of the study support the view that 23 GW represents the limit of the current technology. Nevertheless, management policies could be important for survival of the most immature infants. Studies from Sweden and Germany support that proactive management promotes survival in infants born at 22 to 25 GW (Hakansson et al. 2004, Herber-Jonat et al. 2006).

4.3.2. Neonatal morbidity

Preterm infants are at increased risk of early complications in different organ systems (Table 1). Medical problems are especially prevalent among 22–25 GW infants, since their extremely immature organs at birth ill-equip them to make the transition from intrauterine to extrauterine life (Hakansson et al. 2004, Larroque et al. 2004, Lucey et al. 2004). Although neonatal morbidities in preterm infants are separate clinical entities, they are also strongly correlated. For example, acute lung problems shortly after birth are correlated with circulatory problems, brain haemorrhage, and later lung disease.

Table 1. Common medical problems in VPT infants (modified from Johansson and Cnattigius 2010)

Clinical entity	Synopsis
RDS	Lung problem developing shortly after birth due to lack of endogenous surfactant in the lungs. Surface tension increases in the smallest airways and lungs get non-compliant. Treated with instillation of exogenous surfactant in the airway. Common reason for MV or CPAP treatment.
PDA	The duct is a blood vessel between the pulmonary artery and the aorta, essential for foetal blood circulation. The duct should close after birth but can stay open in preterm infants, shunting too much blood to the lungs and leaving too little blood for other organs. Can be closed with drugs or surgery.

Clinical entity	Synopsis
PIVH	Bleeding originating in the germinal matrix, a highly vascularised and cellularly active tissue beside the brain ventricles. Localised bleedings may not be associated with poor outcome, but those resulting in ventriculomegaly and/or extending into the brain tissue (PIVH grade 3–4 according to the classification by Papile et al. 1978) may have a poor prognosis, and could contribute to decisions to withdraw care (end-of-life decisions).
PVL	Damage of brain white matter, related to hypoxia and inflammation. The initial insults may usually occur shortly after birth or during a sudden clinical deterioration and PVL then develops over the following weeks. Cystic forms of PVL (PVL grade 2, particularly PVL grade 3–4 in accordance with data from de Vries et al.1992) are strongly associated with later low motor function.
Infections	Very common, due to an immature immune system and much exposure to bacteria from the environment (including staff). Bacteria of low virulence and fungi are common pathogens. Can usually be treated successfully with antibiotics but infection-related mortality is significant.
NEC	Inflammation and necrosis of the bowel, leading to various abdominal symptoms. In cases of NEC stage 2 (classification by Bell et al. 1978), treated with bowel rest and antibiotics, but surgical bowel resection is commonly performed in cases of bowel necrosis and/or perforations (NEC stage 3).
BPD	A more chronic lung problem, related to short GA, RDS, PDA, infection, and MV. Months of ventilatory support and supplementary oxygen may be needed in severe cases. For VPT infants, BPD is usually defined as a need for supplemental oxygen at the postnatal age of 28 days (mild BPD), and/or a need for <30% oxygen at 36 weeks of PMA (moderate BPD), and/or a need for ≥30% oxygen and/or positive pressure (MV or CPAP) at 36 weeks of PMA or discharge, whichever comes first (Jobe et al. 2001). Some, but not all, children can be prone to asthma-like problems and have reduced lung function in their future life.
ROP	Overgrowth of blood vessels in the immature retina of the eye, related to factors such as short GA and oxygen administration. By the international classification for ROP (Committee for the Classification of Retinopathy of Prematurity 1984), the disease is divided into five stages. Low-grade retinopathy (ROP stage 1–2), usually resolve without specific therapy but laser treatment may be needed in severe forms (ROP stage ≥3). Worst-case scenario includes retinal detachment and blindness.

Tables 6 and 7, presented in the section of "Results and discussion", provide neonatal morbidity rates among VLGA/VLBW and ELGA/ELBW infants reported in worldwide population-based or multicentre studies.

4.4. Long-term consequences of very preterm birth to the individual

Typical long-term adverse consequences of preterm birth include growth failure, cerebral palsy (CP), poor cognitive performance (usually intelligence quotient (IQ) <70), and vision and hearing impairments.

There is some confusion over the need to correct chronological age for prematurity after birth. It is self-evident that proper assessment of growth and development over the first year must take into account the level of prematurity, and most authorities recommend that the correction has to be continued until 2 years of age. At this age, after birth at 28 GW, correction produces a 12% difference in terms of developmental age. This is an important clinical difference compared with the assessment based on chronological age. For more immature children, this correction could be continued longer than this, as the difference will be significant until 3 years (24 GW: 11% difference). However, by the time a preterm child reaches nursery or school, continuing to make these corrections is then irrelevant and makes only clinically insignificant difference to developmental scores (Marlow 2004).

4.4.1. Growth

A number of studies have shown that the majority of VLBW infants in a NICU develop growth failure with parameters below the 10th percentile by 36 weeks of PMA or by time of discharge from the NICU (Ehrenkranz 2000, Clark et al. 2003) and many remain small into childhood and adolescence (Hack et al. 2003). Impaired head growth and subnormal head size are associated with poor cognitive function and academic achievement at school (Hack et al. 1991a), suggesting a link between postnatal growth and neurodevelopmental potential.

4.4.2. Neurosensory outcome

CP is one of the most common and severe sequelae of VPT birth. VLGA/ VLBW infants are between 20 to 80 times more likely to have CP than infants born at term (Surveillance of Cerebral Palsy in Europe 2000). Controversy exists regarding the trends in prevalence of CP over time. Although some studies have indicated an increase with the falling neonatal mortality (Hagberg et al. 2001, Vincer et al. 2006), and other studies have documented a stable CP rate (Vohr et al. 2005b, Doyle et al. 2011), a number of more recent studies have presented a declining rate of CP in ELBW and VLBW children (Platt et al. 2007, Groenendaal et al. 2010, Serenius et al. 2013).

There have been many assessment schemes for neurological outcome following preterm birth but the outcome measures reported and definitions of disability vary considerably. Key elements of the current CP definitions involve the following features: 1) it is a group of disorders of movement and posture and of motor function; 2) it is permanent but not unchanging; and 3) it is due to a non-progressive interference/lesion/abnormality in the developing/immature brain. A European network of health professionals working in the domain of CP has agreed on this definition (Surveillance of Cerebral Palsy in Europe 2000), which is also in line with a recently proposed international definition (Rosenbaum et al. 2007). Of the different patterns of CP, spastic diplegia is that most typically associated with preterm birth. It is generally thought to be the con-

sequence of injury to the descending motor pathways, in which those fibres supplying the lower limb are more prone to bilateral hypoxic-ischaemia, and is associated with PVL. Hemiplegia and more complex spastic CP may occur, but less commonly and result from more extensive lesions including the cortex. In particular, hemiplegia may arise following haemorrhagic periventricular infarction, associated with PIVH. The most immature children may have very complex motor disability with injury to multiple areas (Fawke 2007).

A diagnosis of CP does not equate to severe disability nor does not having CP mean that no disabilities are present. Therefore, functional outcome measures are important, as they give a richer picture of child's abilities (Fawke 2007). In the 1990s a validated scale – the Gross Motor Function Classification System (GMFCS) – became available for assessing bimanual function and gross motor function in young children with CP (Palisano et al. 1997).

Severe problems in sensory deficits are diagnosed during the first years of life, whereas again, significant disability from visual or hearing loss is GA dependent and rates are moderately consistent across cohorts. Poor visual perception in EPT Swedish children born in the early 1990s was five times as common as in full-term (FT) controls (21 vs. 4%) (Finnstrom et al. 1998). The importance of the contribution of ROP to severe visual loss has become clearer in the cohorts born since systematic screening was introduced. However, although the increased survival of the more susceptible infants has meant that rates and absolute numbers of ROP needing treatment are on the increase, gestation specific rates of severe visual impairment over the last decades have decreased (Vohr et al. 2005b, Doyle et al. 2011) which may reflect the efficacy of ROP screening programmes.

The rates of CP, blindness, and deafness in population-based and multicentre cohorts of VLGA/VLBW and ELGA/ELBW infants are shown in Tables 13 and 14 in the section of "Results and discussion".

4.4.3. Cognitive and behavioural outcomes

Despite the perceived importance of CP, the most common outcome disability at 2 years of CA is developmental or cognitive impairment, which assumes greater significance in the school years (Marlow 2004).

Standardised developmental assessments are important in the early detection of developmental delay in children, determining eligibility for early intervention programmes and the evaluation of perinatal and neonatal treatment. The need for objective measures has led to the widespread use of standardised IQ tests as indicators of outcome. IQ tests are psychometric measures that yield standardised scores on a normalised distribution (typically mean = 100, standard deviation (SD) = 15) and are thus statistically comparable. Although VLGA/VLBW children typically have group mean IQ scores within the normal range (±1 SD), these are significantly lower than their FT counterparts (Bode et al. 2009, Anderson et al. 2010), even for those who are free of severe disability (Charkaluk et al. 2010). A meta-analysis of outcome for VLGA/VLBW child-

ren aged 5–14 years pooled data from 15 high-quality studies (Bhutta et al. 2002). Weighted mean differences for individual studies ranged from 7.0 to 22.7 points, with an aggregate weighted mean difference of 10.9 IQ points (95% confidence interval (CI) 9.2–12.5) between VLGA/VLBW children and FT controls. Results were unaffected by country, age at assessment, and regional versus hospital-based cohorts. The highest weighted mean differences were found for studies in which children with severe neurosensory impairments were included. The deficit in IQ for ELGA/ELBW children is larger than that for VLGA/VLBW cohorts. A regional cohort of ELBW (BW <750 g) children scored 13 points lower than FT controls and 6 points lower than low BW controls matched for age, sex, and ethnic group (Hack et al. 1994). Follow-up data for young ages are now beginning to emerge for cohorts born in the 2000s (Bode et al. 2009, Anderson et al. 2010, Munck et al. 2010, Doyle et al. 2011, Rattihalli et al. 2011, Serenius et al. 2013) and continue to highlight the cognitive disadvantage in these populations. Within-group analyses for VPT children have shown a correlation between IQ and GA. Bhutta et al. identified a linear relationship between GA and IQ from 25 to 40 GW (Bhutta et al. 2002).

While there is no criterion standard for determining developmental delay (Johnson and Marlow 2006, Aylward 2009), the Bayley Scales of Infant Development (BSID) (Bayley 1969) and its revisions – BSID-II and BSID-III – (Bayley 1993, Bayley 2006) are the most widely reported measures. BSID-II has been used in many studies to determine rates of developmental delay in VPT children and perinatal factors associated with poor outcome (Wood et al. 2000, Vohr et al. 2005b, De Groote et al. 2007, Wilson-Costello et al. 2007, Munck et al. 2010). The primary scales from the BSID and BSID-II are the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI). In brief, the MDI evaluates early cognitive and language development, while the PDI evaluates early fine and gross motor development. The broad natures of both the MDI and PDI are the main limitations of the BSID and BSID-II. For example, low MDI scores may reflect a specific delay in communication skills, cognitive abilities, or both. BSID-III attempts to address this limitation by refining the measure to include separate composite scores for cognitive, language, and motor domains. In addition, scale scores can be calculated to assess receptive communication, expressive communication, and fine and gross motor development. Thus, the structure of the new BSID-III has the potential to provide more clinically useful information relating to early development, improving the capacity to discriminate specific developmental problems and helping to target early intervention programmes to more specific areas of weakness. The majority of studies have demonstrated that EPT and VPT infants obtain lower scores on the BSID–II MDI, as well as on PDI, when compared with a FT control group at 24 months of age (Munck et al. 2010, Voigt et al. 2012). To date, the first published studies have used the BSID-III (Bode et al. 2009, Doyle et al. 2011, Janssen et al. 2011, Serenius et al. 2013), and the original enthusiasm for this measure may have waned, with many clinicians

suggesting that it overestimates development and, as such, underestimates delay (Anderson et al. 2010, Moore et al. 2012).

Behavioural and other psychological outcomes seem to be equally problematic (Marlow 2004). The VPT child is at increased risk for subclinical behavioural problems and can most often be described as inattentive, shy or withdrawn, and with poor social skills. VPT children are more likely to have psychiatric disorders, of which attention deficit and hyperactivity disorders are the primary abnormal outcome. There is also some evidence of increased risk for Autistic Spectrum Disorders in VPT children (Johnson 2007, Schendel and Bhasin 2008).

Neurodevelopmental impairment (NDI) is a well-known definition for describing combined outcome for VPT infants. Usually NDI is defined as the presence of CP, delayed mental development (MDI >2 SD below the mean), severe hearing impairment, and/or severe visual impairment (Bode et al. 2009, Munck et al. 2010).

4.4.4. Respiratory outcome

Chronic respiratory diseases are a common complication of preterm birth, particularly among very immature infants or those suffering from BPD (Jobe and Bancalari 2001). Lung injury and the subsequent maladaptive repair process that leads to the development of chronic lung problems are complex, with numerous factors (for example, degree of immaturity, BPD, inflammatory mediators, atypical pathogens, recurrent viral infections) interacting to determine outcome (Kwinta and Pietrzyk 2010). Preterm infants with BPD may require supplementary oxygen for many months or even years (Greenough et al. 2002), although few remain oxygen dependent beyond 2 years of age (Greenough et al. 2006). Infants requiring supplementary oxygen at home have the most severe lung disease, as evidenced by their need for hospital readmission in the first two years after birth being twice that of those with BPD who are not oxygen dependent (Greenough et al. 2002).

The major respiratory problem in infancy and early childhood is respiratory exacerbations caused by infection, particularly viral ones (Kwinta and Pietrzyk 2010). While acute respiratory morbidity in infants born FT is relatively well studied, in contrast, data for VPT infants, especially during post-surfactant era, are scarce. Previous studies have shown that premature infants are more susceptible to acute respiratory infections (RI) than FT infants, having more wheezing episodes and hospital readmissions due to respiratory problems in the first two years of life (Lamarche-Vadel et al. 2004, Smith et al. 2004, Bhandari and Panitch 2006, Holditch-Davis et al. 2008, Kwinta and Pietrzyk 2010, Pramana et al. 2011). Moreover, they are more likely to die during infancy from acute lower respiratory tract infections than other infants (Holman et al. 2003). Hospitalisation rates decline after the 2nd year of life and are infrequent in 14-year-old children who had been born preterm regardless of their BPD status (Doyle et al. 2001).

The chronic respiratory symptoms become mild in school-age children (Filippone et al. 2009). However, for some preterm infants, particularly those with BPD, obstructive lung disease persists into adulthood (Northway et al. 1990). Prematurity is associated with an increased risk of asthma from childhood to adulthood. In a population-based register study in Finland, a substantially increased risk of asthma was observed for premature children compared with the risk for FT and normal-weight children, whereas two thirds of the cases were diagnosed before the age of 3 years (Metsala et al. 2008). The association between prematurity and asthma has been explained, firstly, by the fact that prematurity causes reduced lung growth and reduced airway calibre, which may increase wheezing symptoms during RI and in turn increase asthma diagnose, and secondly, because prematurity may predispose the child to respiratory tract infections, which would further strengthen these associations.

4.4.5. Adult outcome

With regard to preterm birth and outcomes in adulthood, we need to consider that modern neonatal intensive care has a short history. Consequently, very little is known about health in adult life for the growing number of children who have survived VPT and EPT birth since the 1990s. Follow-up studies of adults born VPT predominantly include individuals born during the late 1970s and early 1980s (Saigal et al. 2006, Lindstrom et al. 2007, Moster et al. 2008). The results from cohort studies of EPT infants for which there was a FT or normal BW group for comparison have shown that in early adulthood as a group, survivors of extreme prematurity have higher rates of many adverse health outcomes compared to FT controls: for example, a higher risk of neurological impairments, low vision, epilepsy, hearing loss (Saigal et al. 2006, Moster et al. 2008), poor education and employment (Lindstrom et al. 2007), and disorders of psychological development, behaviour, and emotion (Moster et al. 2008). Even among those who were recorded as not having medical disabilities, the proportions of people who achieved higher education, held well-paying jobs, established a family, had biological children, and did not receive social security benefits were lower (Moster et al. 2008).

4.5. Consequences of very preterm birth on families and to the society

Clearly, from all studies, prematurity and its associated sequelae have an enormous negative psychological and emotional effect on the family (Cronin et al. 1995, Singer et al. 1999, Taylor et al. 2001, Moore et al. 2006). The effect of psychological and emotional distress was greatest for VLBW high-risk infants in the first month of life and persisted during the first two years of life. By the age of 3 years, parenting stress remained greater for VPT infants than for normal BW infants (Singer et al. 1999). The effect seems to vary according to

medical risk factors, developmental outcome, family environment and income, parental education, and child's age at reporting (Cronin et al. 1995, Singer et al. 1999, Taylor et al. 2001, Moore et al. 2006).

The financial burden of prematurity to the society is significant. Several studies have demonstrated that preterm births contribute disproportionately to overall delivery costs, accounting for a small percentage of discharges, but approximately half of all costs (Schmitt et al. 2006, Russell et al. 2007). One example appears in a study (Russell et al. 2007) where 8% of all births included a diagnosis of preterm birth or low BW, yet these accounted for 47% of the total costs. Thus, the costs of the initial hospitalisation in VPT infants are high, and the costs along with the length of stay increase with decreasing GA or BW (Phibbs and Schmitt 2006). In addition to the long initial hospitalisation, the need for hospital inpatient and outpatient care remains substantial during the first years of life in VPT children (Gray et al. 2006).

There are few studies on the use of healthcare resources reaching beyond the first year of life and beyond childhood in the preterm population. For example, Leijon et al. have shown that there were no significant differences in visits to a general practitioner between VPT infants and FT controls during the first four years of life (Leijon et al. 2003). However, during the first year of life, 67% of VPT infants had visits to specialists, versus 26% of FT controls. Between 1 to 4 years of age, the respective figures were 74 vs. 45% (Leijon et al. 2003). In a Finnish study, the healthcare costs during the fifth year of life in VPT children with morbidities were 4.4-fold and in those without morbidities 1.4-fold compared with those of FT control subjects (Korvenranta et al. 2010). In contrast, Saigal et al. showed that the use of health-care resources in ELBW infants in young adulthood in terms of hospitalisations, surgical procedures, visits to specialists, or in the use of rehabilitative services were not significantly different compared to FT controls (Saigal et al. 2007).

Assessing the costs of the care of VPT infants in terms of quality-adjusted life years (QALY) enables to describe the cost-effectiveness of care. The cost per QALY in preterm children has been evaluated by Cutler and Meara (Cutler and Meara 1999). This study was based on estimations from different studies and suggested a cost per QALY of $6,101 for those born with BW below 1000 g and $1,290 for those weighing 1000–1500 g at birth, assuming that the children reach 50 years of age. Although there is no absolute cut-off, in the Unites States tends to be general consensus that treatments with a cost-effectiveness ratio of $50,000 to $100,000 per year of life gained are acceptable (Talmor et al. 2006). Consequently, the study by Cutler and Mara indicated that the benefit of treatment of prematurity was so large that it dwarfed all the uncertainties inherent in the data (Cutler and Meara 1999).

4.6. Factors impacting on outcomes in very preterm infants

Factors contributing to the outcome of VPT infants include the characteristics presented in Table 2.

Table 2. Spectrum of factors contributing to outcomes of VPT infants (modified from Vohr 2010)

	Characteristics
Intrauterine environment	Maternal infection and hypertension, drug exposure, smoking, and multiple gestation
Perinatal and neonatal interventions	Delivery in tertiary centres, timing of delivery and use of antibiotics, administration of antenatal corticosteroids, delivery by caesarean section, surfactant replacement therapy, use of MV or non-invasive respiratory support and oxygen supplementation beyond stabilisation, management of PDA, postnatal corticosteroids, nutrition and growth
Neonatal characteristics and morbidities	Extreme prematurity, gender, PIVH, PVL, BPD, NEC, sepsis, ROP
Post-discharge environment	Maternal education, family income, health insurance, early intervention services
Post-discharge healthcare needs	BPD, anaemia, osteopenia, hernias, recurrent hospitalisation
Comorbidities	Congenital anomalies, CP, vision and hearing impairment

4.6.1. Intrauterine environment

Inflammatory mechanisms are known to be associated with preterm birth and neonatal morbidities. Proinflammatory cytokines in amniotic fluid and in foetal blood appear to increase the risk of neonatal brain injury and adverse long-term outcome. Associations have been reported between antenatal infection, a foetal inflammatory response, vasculitis, PPROM, white matter damage, and long-term disability (Dammann et al. 2001, Dammann et al. 2002, Yoon et al. 2003, Beaino et al. 2010). Two maternal complications associated with inflammation and infection, chorioamnionitis and PPROM, are associated with the development of PVL. In a report examining the association between histological chorioamnionitis and PVL, severe inflammation in the umbilical cord was observed in 53% of infants with PVL and 32% without PVL ($p < 0.05$) (Wharton et al. 2004). In turn, PVL is strongly associated with an increased rate of CP and associated morbidities (Perlman 1998). In a systematic review and meta-analysis with the aim to find associations between chorioamnionitis and ROP in preterm infants, unadjusted analyses showed that chorioamnionitis was signifi-

cantly associated with ROP as well as with severe ROP. However, the association disappeared on analysis of studies adjusting for GA (Mitra et al. 2014). Also the clinical research on relationships between chorioamnionitis and RDS and BPD remains unsettled (Jobe 2011).

Few studies have addressed antenatal risk factors for cognitive developmental impairment. Helderman et al. have shown in a cohort of ELGA infants surviving at 2 years of CA that maternal obesity and one placental finding – thrombosis of foetal stem vessels – were associated with impaired early cognitive function (Helderman et al. 2012).

Multiple pregnancies are often complicated by increased maternal complications, preterm delivery, perinatal complications, intrauterine growth restriction (Donovan et al. 1998), and increased rates of adverse neurodevelopmental outcomes (Pharoah 2002).

4.6.2. Perinatal and neonatal interventions

Delivery in tertiary centres and the effect of regionalisation

Many studies have concluded that the risk of neonatal death is lower when a VPT birth occurs in a maternity unit with an onsite NICU (Ozminkowski et al. 1988, Lasswell et al. 2010). This result is attributed to differences in the quality of care, the concentration of technical expertise, and coordination between obstetrical and neonatal teams in tertiary level perinatal units as well as to the deleterious effects of transporting immature newborns in an ambulance after birth to an intensive care unit (Smith et al. 1990). Even in healthcare with well organised transport systems, the mortality and morbidity of immature inborn infants are lower than those of outborn infants who are transported after delivery (Palmer et al. 2005, Rautava et al. 2007, Mohamed and Aly 2010), and decrease further at hospitals with higher volumes of patients and higher levels of care (Phibbs et al. 2007). Although Watson and his colleagues did not find evidence for an association between inter-facility transport and PIVH or mortality among VLBW infants after accounting for potential confounders, there was an independent association between the overall clinical status of the infant, PIVH, and inborn vs. outborn status (Watson et al. 2013).

Two meta-analyses have summarised the results of the literature on the effects of the regionalisation. Ozminkowski et al. (Ozminkowski et al. 1988) meta-analysis included 19 non-randomised studies, and the results showed strong preferences for inborn status, especially for infants weighing between 1001–2000 g. Lasswell (Lasswell et al. 2010) included 41 studies on VPT infants. Adjusted odds ratio (OR) of death for VPT infants was 1.55 (95% CI 1.21–1.98) if born outside of tertiary level unit. No change over time was found according to year of publication. Some studies have found that the benefits of delivering in tertiary level structures are greatest for EPT infants (Lee et al. 2003, Johansson et al. 2004), but this result has not been found elsewhere (Empana et al. 2003). Concerning the long-term outcome, Rautava et al.

(Rautava et al. 2013) have shown that long-term health outcomes for EPT infants are better if they receive their whole initial neonatal care in tertiary units.

National recommendations about delivery of VPT infants in tertiary centres exist in many countries. The American Academy of Paediatrics recommends that deliveries at <32 GW take place in specialised units (Stark 2004) and most European countries have passed laws or issued recommendations based on this premise (Zeitlin et al. 2004). In Estonia, there is a general consensus of professional societies to regionalise the births before 34 GW.

Timing of delivery and use of antibiotics

Preterm delivery can be delayed by using tocolytic drugs and antibiotics in the case of PPROM. Tocolysis prolongs gestation and allows other antenatal interventions, such as antenatal steroids and centralisation of care, to be fully implemented. In Sweden, tocolysis was associated with both significantly increased survival and a doubled chance of one-year survival without severe neonatal morbidity (Fellman et al. 2009, Haas et al. 2012). Magnesium sulphate given to women at risk of imminent preterm birth has been shown to reduce the incidence of CP (Doyle et al. 2009). Progesterone supplementation may delay preterm birth in women with a history of previous preterm delivery and those with a short cervix (Rode et al. 2009).

PPROM is responsible for approximately one third of all preterm births (Stringer et al. 2004). During management of PPROM, physicians must balance the risk of RDS and other sequelae of premature delivery with the risks of pregnancy prolongation, such as neonatal sepsis and cord accidents (Medina and Hill 2006). Therefore antibiotic therapy for women in PPROM at 34 GW or less is a routine practice to delay labour and reduce neonatal morbidity. Meta-analyses support positive effect of antibiotic therapy in some short-term outcomes (Hutzal et al. 2008, Kenyon et al. 2010) such as reduction in chorioamnionitis and in infants' morbidity markers (neonatal infection, use of surfactant, oxygen therapy, and abnormal cerebral ultrasound scan prior to discharge from hospital). However, evidence is not conclusive for long-term outcomes.

Administration of antenatal corticosteroids

Significant evidence has accumulated in clinical trials of the beneficial effects of antenatal steroid administration in improving survival and decreasing the incidence of RDS, PIVH, PVL, NEC, and early systemic infections among preterm infants (Wright et al. 1995, Roberts and Dalziel 2006, Carlo et al. 2011). Prenatal steroids given to women with anticipated preterm delivery reduce the risk of neonatal death (relative risk, 0.55; 95% CI 0.43–0.72; number needed to treat = 9), and the use of a single course of antenatal steroids does not appear to be associated with any significant maternal or short-term foetal adverse effects (Roberts and Dalziel 2006). Antenatal corticosteroid therapy is recommended in all pregnancies with threatened preterm labour between 24 and 34 GW by the American Congress of Obstetricians and Gynaecologists Committee (ACOG Committee on Obstetric Practice 2011). Effects of multiple

courses of steroids on foetal growth have raised concerns about recommending more than a single additional rescue course (Peltoniemi et al. 2011). However, further information is required concerning optimal dose to delivery interval, optimal corticosteroid to use, effects in multiple pregnancies, and to confirm the long-term effects into adulthood (Roberts and Dalziel 2006).

In multivariate analyses, antenatal steroids are consistently the only antenatal intervention contributing to the decreased rates of CP (Vohr et al. 2005b) and NDI (Vohr et al. 2000, Carlo et. al. 2011).

Delivery by caesarean section

The optimal mode of delivery for women thought to be in labour and at high-risk of delivering a small baby is controversial. No randomised controlled trial has compared route of delivery in preterm infants, but observational studies support an improved outcome with the use of caesarean delivery. In a review of linked birth and infant death certificates from 2000 to 2003, Malloy reports a significant reduction in neonatal mortality for infants delivered by caesarean at 22 to 25 GW (Malloy 2008). Caesarean section had been proposed in preterm labour in order to reduce the infant's morbidity and mortality, but is associated with maternal morbidity (Grant and Glazener 2001). However, a study from Europe showed a large variability of caesarean section rates (from 29 to 84%) for infants born between 28 and 31 GW without correlation to detected morbidity and mortality, with the exception of pregnancies with hypertension and foetal growth restriction (Zeitlin et al. 2010b).

Surfactant replacement therapy

Surfactant replacement therapy has reduced mortality and several aspects of morbidity in newborns with RDS and is nowadays a standard treatment in VPT infants with RDS (Sweet et al. 2013). Surfactant replacement therapy is crucial in the management of RDS, but the best preparation, optimal dose and timing (prophylactic vs. selective) of administration at different gestations are not always clear (Sweet et al. 2013). For many years, surfactant prophylaxis for EPT infants was considered to offer the best chance of survival (Soll and Morley 2001). More recent clinical trials show that with a policy of early initiation of CPAP and selective surfactant administration (rather than routine prophylaxis) babies may do better with reduced rates of death or chronic lung disease in the CPAP group (Rojas-Reyes et al. 2012). MV can be avoided by using the "INSURE" (INtubate – SURfactant – Extubate to CPAP) technique and this method has been shown in randomised trials to reduce the need for MV and subsequent BPD (Stevens et al. 2007).

Use of MV or non-invasive respiratory support and oxygen supplementation beyond stabilisation

MV is associated with significant short- and long-term morbidity in VPT infants and should be used to support babies when other methods of respiratory support have failed (Sweet et al. 2013). Nowadays most of the evidence suggests that

non-invasive respiratory support is a viable alternative to MV in many preterm infants. Non-invasive respiratory support can be defined as any form of respiratory support that is not delivered via an endotracheal tube. It includes CPAP, various types of ventilation provided through soft nasal prongs or masks which are collectively called "nasal intermittent positive pressure ventilation", and humidified oxygen delivered by high-flow nasal cannulae (Bancalari and Claure 2013). Consequently, avoidance of MV by means of early CPAP with or without surfactant administration may still be the most effective way to reduce the risk of lung injury (Sweet et al. 2013). There are clear links between MV through an endotracheal tube and subsequent development of BPD and neurodevelopmental sequelae (Philip 2012). Although the degree of immaturity is by far the most important risk factor for ROP, prolonged oxygen dependency and a longer duration of MV are also found to be important risk factors for severe ROP (EXPRESS Group 2010, Chen et al. 2011). Strict monitoring and administration of oxygen is crucial for decreasing the incidence of ROP. Presently, studies are being performed to determine the optimal level of oxygen supplementation to further decrease the risk (Sears et al. 2009). Excess supplemental oxygen exposure is to a lesser extent also linked with development of BPD (Saugstad 2007, Chen et al. 2011).

Management of PDA

The failure of ductus closure can induce hemodynamic effects if blood is shunted from the systemic circulation to the pulmonary circulation. The resulting pulmonary over-perfusion increases the risk of BPD and the systemic hypoperfusion may increase the risk of NEC, renal failure, and PIVH/PVL (Chiruvolu and Jaleel 2009). Although there are several papers addressing important issues on prevention (restricted vs. liberal water intake, pharmacological closure) (Bell and Acarregui 2008, Fowlie et al. 2010) and treatment of PDA (Shah and Ohlsson 2006, Malviya et al. 2008), a review in 2010 concludes that trials using current management of PDA are not justified (Benitz 2010). Additionally, despite two multicentre trials having shown a beneficial effect of prophylactic indomethacin, no differences in CP and NDI at 2–4 years of age were obtained (Ment et al. 1994, Ment et al. 2000, Schmidt et al. 2001). There is an observational association between surgical ligation and an increased risk of long-term adverse effects; however, it is not clear if this is a direct result of surgery or due to complications incurred while waiting for it (Malviya et al. 2008).

Postnatal steroids

Corticosteroids have powerful anti-inflammatory effects. After initial reports indicated the beneficial effects of postnatal steroids for ventilator-dependent infants, administration to VPT infants became almost universal for BPD (Cummings et al. 1989). However, it is unclear whether any beneficial effects outweigh the adverse effects of these drugs. The reports of Yeh et al. (Yeh et al. 1997, Yeh et al. 1998) first established a link between postnatal steroid admi-

nistration and adverse motor outcomes. In addition, adverse effects on cognitive function at school age have also been reported (Yeh et al. 2004). The American Academy of Paediatrics (Watterberg 2010) has recommended against the routine use of systemic steroids to treat or prevent BPD, and stated that evidence is insufficient to recommend both low dose dexamethasone or hydrocortisone and invite clinicians to make individualised decisions in conjunction with the infant's parents. Recent reviews continue to discourage the use of hydrocortisone in chronically ventilator-dependent infants with established or evolving BPD (Doyle et al. 2010).

Nutrition and growth

Maternal breast milk remains the choice of enteral nutrition for preterm infants according to observational studies and meta-analyses, whereas breast milk is beneficial for VPT infants for the same reasons as for FT infants (Callen and Pinelli 2005, Lucas 2005). Additionally, breast milk may confer protection against NEC (Callen and Pinelli 2005) and contribute to neurological development (Lucas 2005). Furthermore, breastfeeding represents an opportunity to involve mothers in infant care during hospitalisation and to encourage mother-child bonding (Flacking et al. 2006). There are no data from randomised controlled trials to determine whether feeding preterm infants with nutrient-enriched formula milk versus human breast milk affects growth and development as it seems very difficult and probably unethical to randomise infants to receive maternal versus formula milk. (Henderson et al. 2007). The limited available data suggest that feeding preterm infants following hospital discharge with multinutrient fortified breast milk compared with unfortified breast milk increases growth rates during infancy (McCormick et al. 2010).

Several recent reports have indicated that poor postnatal weight gain (Fortes Filho et al. 2009, EXPRESS Group 2010) and low serum insulin-like growth factor 1 levels (Hellstrom et al. 2003) are predictors for neonatal morbidities, for example, for ROP.

4.6.3. Neonatal characteristics and morbidities

Extreme prematurity and gender

Mortality in VPT infants is inversely related to GA. Numerous studies show that low GA and BW (Tommiska et al. 2001; Vanhaesebrouck et al. 2004, Evans et al. 2007; Itabashi et al. 2009) are risk factors for perinatal and neonatal deaths in VPT infants; whereas the more growth restricted the infant, the greater is the risk of mortality (Evans et al. 2007). Similar to mortality, morbidity risks are inversely related to GA. Compared to FT infants, VPT commonly suffer from multiple and interacting morbidities (listed in Table 1) whereas medical problems are especially prevalent among infants born at 22–25 GW. The rates of mortality and morbidity in population-based and multicentre cohorts of

ELGA/ELBW infants are shown in Tables 7 and 14 in the section of "Results and discussion".

Premature males are at a significantly increased risk of neonatal death, in-hospital morbidity (Stevenson et al. 2000), and poor neurodevelopmental outcomes (Vohr et al. 2000). The neonatal and neurodevelopmental outcomes at 18–22 months' CA were evaluated in a large cohort of ELBW boys and girls born in 1997 to 2000 (Hintz et al. 2006). Girls were more likely to survive (67%) than boys (58%) and boys were more likely to have BPD, PIVH grade 3–4, and ROP stage ≥3. Additionally, boys were significantly more likely to have a MDI <70 (42 vs. 27% for girls), CP, low PDI, and NDI.

PIVH and PVL

Brain injury that occurs in association with severe PIVH grade 3–4, PVL, ventriculomegaly, or white matter injury has consistently been demonstrated to be associated with poor developmental and neuromotor outcomes. In a number of large cohort studies of VPT infants PIVH grade 3–4 and PVL have been independently associated with NDI at 18–22 months of age after adjusting for known confounders, and, in fact, the majority of neonates with these findings do develop neurological sequelae (Vohr et al. 2000). In the international multicentre outcome study of ELBW infants reported by Schmidt et al. (Schmidt et al. 2003), among infants with brain injury (defined as the presence of echodense intraparenchymal lesions, PVL, porencephalic cysts, ventriculomegaly with or without PIVH, and PIVH grade 3–4 on neonatal ultrasound scanning) 42% had a MDI <70 compared with 23% of infants who had no evidence of brain injury. Infants with brain injury also had increased rates of CP (36 vs. 7%) compared to infants with no brain injury.

Beaino et al. assessed in a prognostic manner, the associations between a detailed set of obstetric and neonatal risk factors and CP in a large population-based cohort of VPT infants and found that cerebral lesions on neonatal ultrasound screening were the most important predictors of CP in VPT infants. In particular, after adjustment for other factors, the odds of developing CP were increased 30-fold in infants with cystic PVL or intraparenchymal haemorrhage (Beaino et al. 2010).

BPD

Northway et al. (Northway et al. 1990) have re-evaluated pulmonary function in their original cohort of infants with severe BPD reported in 1967. These young adults still exhibited some evidence of pulmonary dysfunction comprising airway obstruction and hyperactivity as well as hyperinflation. Nowadays, the outcome of infants with BPD has improved, in part because of better management, but mainly because of the milder presentation of the disease. Nevertheless, pulmonary function studies of infants with a history of BPD indicate that pulmonary function may be impaired for many years even though the infants may be asymptomatic (Jobe 2011).

Infants with BPD also exhibit impaired growth curves and have more neurodevelopmental sequelae when compared with similar control groups. Schmidt et al. (Schmidt et al. 2003) reported the rate of low cognitive function at 18 months of CA in ELBW children with BPD. Children with BPD were more likely to have an MDI <70 (36 vs. 19%), CP (17 vs. 9.3%), and deafness (3.5 vs. 1.4%) compared with ELBW children with no BPD.

NEC

In a multicentre study of ELBW infants, increased severity of NEC was associated with higher mortality and longer duration of hospitalisation. At 18–22 months of CA, infants who had surgically managed NEC had higher rates of MDI <70, PDI <70, and NDI (44, 37, and 57%, respectively) than those managed medically (37, 25, and 44%), or those without NEC (31, 19, and 40%) (Hintz et al. 2005). Regression analyses showed that surgical NEC was associated with significantly larger proportion of children with MDI <70, PDI <70, NDI, and growth failure at 2 years of CA.

Sepsis

Sepsis is not only a major cause of death after the first week of life but it also prolongs the duration of MV, disrupts nutrition and growth, triggers other neonatal co-morbidities such as PDA, BPD, and ROP (Stoll et al. 2004, Liu et al. 2005), and increases the risk for later disability. Stoll et al. found that compared with uninfected infants, those with neonatal infection were significantly more likely to have adverse neurodevelopmental outcome at follow-up, including CP (range of significant ORs, 1.4–1.7) (Stoll et al. 2004). A report from the United Kingdom noted a 4-fold increase in CP among VLBW infants with a history of neonatal sepsis compared with infants with no history of neonatal infection (Wheater and Rennie 2000).

ROP

ROP is one of the significant predictors of poor neurodevelopmental outcome. The children involved in the CRYO-ROP (Cryotherapy for Retinopathy of Prematurity) multicentre study were initially evaluated at 5.5 years. Rates of severe disability increased from 3.7% for those children with no ROP to 19.7% for those with threshold ROP (Msall et al. 2000). A subgroup of the children with threshold ROP was re-evaluated at 8 years of age. Overall, 70% of children with an unfavourable vision outcome and 56% with a favourable outcome had a neurodevelopmental, behavioural, or learning disorder (Msall et al. 2004). Although rates of NDI were high for both groups of children with a history of threshold ROP, it was the group of children with vision impairment at 8 years who were more likely to have multiple morbidities.

4.6.4. Post-discharge environment, post-discharge healthcare needs, and comorbidities

When examining predictors of outcomes, environmental factors, including maternal education, race, family income, health insurance, and exposure in intervention services, have all been shown to have an impact on cognitive outcome (Vohr 2010). Although a disadvantaged environment is well known to be associated with higher rates of cognitive impairment, children born VPT from high socioeconomic backgrounds still have, approximately, a 10-point reduction in IQ compared to FT controls (Hack et al. 1995).

The benefits of an enriched home environment are clear. Data from the Infant Health and Development Programme demonstrate that infants who receive early intervention have developmental scores significantly higher than infants in the control group who received standard care. Early childhood development programmes have been associated with reductions in grade retention and placement in special education (Stewart 2008).

After discharge, VPT infants are at increased risk of continued complex medical morbidities, including BPD, requiring home oxygen or ventilator management, gastrointestinal reflux disease, poor feeding, and growth failure. Special healthcare needs, which present themselves in the NICU, may persist and increase with increasing age. Hack et al. (Hack et al. 2005a) evaluated a cohort of ELBW infants born in 1992–1995 at 8 years of age. Compared to age- and gender-matched controls, ELBW infants had more asthma requiring therapy (21 vs. 9%), took more regular prescribed medications (37 vs. 19%), were hospitalised more often after the neonatal period (23 vs. 6%), received some type of specialised services such as physical or occupational therapy (31 vs. 3%), and had an individualised education plan (39 vs. 9%). Therefore, VPT infants should have a comprehensive evaluation by a multidisciplinary team to establish an informed clinical opinion to determine, first, their health and development, and second, whether early intervention services are needed (British Association of Perinatal Medicine 2008).

Most follow-up studies exclude infants with major congenital anomalies from their study sample. The neurodevelopmental outcomes of VPT infants with anomalies are needed, however, both for counselling parents regarding outcomes and for facilitation of appropriate support and intervention services. The cognitive outcomes of ELBW infants with major anomalies were evaluated in a large cohort of ELBW infants cared for in the National Institute of Child Health and Human Development Neonatal Network centres (Walden et al. 2007). At the 18–22 month follow-up, a greater percentage of children in the anomaly group had MDI scores <70 (57 vs. 31%), PDI scores <70 (48 vs. 20%), moderate to severe CP (18 vs. 6%), and NDI (65 vs. 37%). Regression models adjusting for confounders indicated that infants with severe anomalies had nearly twice the risk of having MDI or PDI scores <70 compared to ELBW infants without anomalies (Walden et al. 2007).

Preterm infants with CP have associated cognitive impairment. A cohort of ELBW infants participating in the National Institute of Child Health and Human Development Neonatal Network was categorised by neurological status and type of CP at 18–24 months' CA (Vohr et al. 2005a). There was a significant amount of IQ score variability by type of CP: 96% of children with quadriplegia had MDI <70, whereas the respective figure for children with hemiplegia was 41%, with diplegia 69%, and with hypotonic CP 84%.

4.7. Evaluation and improvement of the quality of perinatal and neonatal intensive care for very preterm infants

Neonatal intensive care is expensive. The cost is measured not only in financial terms, but also by the burden of illness caused by the inability to fund alternative healthcare programmes that have to be foregone to finance neonatal intensive care. For those responsible within the healthcare system, including those who treat the babies directly, it is obviously vital to evaluate neonatal intensive care for VPT infants thoroughly.

Effectiveness, efficiency, and availability of neonatal intensive care

Sinclair et al. (Sinclair et al. 1981), in their landmark paper on the evaluation of neonatal intensive care programmes, wrote in 1981: "… the overall effectiveness of these programmes has not been tested experimentally…" and "We conclude that neonatal intensive care programmes require further evaluation with rigorous scientific methods". In the 30 years since their comments, the need for evaluation of neonatal intensive care programmes has not diminished; indeed, it has increased because intensive care has been offered to more EPT at considerable cost to health budgets (Doyle 2006).

Sinclair et al. (Sinclair et al. 1981) described four steps required to evaluate neonatal intensive care programmes: efficacy, effectiveness, efficiency, and availability. Efficacy asks whether a program works under ideal conditions, in contrast with effectiveness, which investigates whether a programme works under normal or "field" conditions. Efficiency assesses whether the programme is worth implementing, and availability examines whether the programme is reaching those who need it.

Despite the lack of randomised controlled trials of complete neonatal intensive care programmes, Sinclair et al. (Sinclair et al. 1981) indicated that subexperimental studies, such as cohort studies, had provided some data on effectiveness. Ideally, effectiveness, efficiency, and availability all should be evaluated within the geographically defined regions that are served by the programme (Doyle 2006).

Data sources for evaluation and improvement: why, when, and how should neonatal outcomes be reported?

Regular follow-up and assessment are important for identifying the particular needs of any individual VPT child. However, there are additionally two major reasons for collecting perinatal, neonatal, and follow-up data on all survivors of VPT birth – to describe the type and incidence of disabilities at any particular age and to relate these to the aspects of care in the perinatal period (Lyon 2007). Additionally, Nuffield Council on Bioethics recommends that in a high-risk pregnancy, or when an unexpected EPT/VPT birth, parents receive up-to-date and consistent information that will inform their decision-making whether before birth, immediately after birth, or in the neonatal period. Information given should include the likelihood of their baby surviving based on the most up-to-date national and local survival rates, potential risks of disability, and the long-term consequences of the decisions made (Nuffield Council on Bioethics 2006).

It is essential that quality improvement be data driven. As a first step to quality improvement, data are used to determine one's baseline performance relative to a set of standards. As one begins to implement changes, data are used to track improvement. Linking aspects of perinatal care to longer-term outcome require the collection of relevant data during the neonatal period and at follow-up.

What is needed is a method of ongoing surveillance of outcome that (Lyon 2007):

- is easy to apply to all VPT infants;
- is relatively cheap;
- can link outcome to current perinatal care;
- can report rapidly so that findings are relevant to current methods of care.

Short-term outcome data

There are two potential sources of short-term outcome data regarding VPT patients: primary and secondary databases. Primary databases – locally designed neonatal databases and (inter)national neonatal networks – are specifically created to address perinatal issues whereas secondary databases were originally designed for other purposes (Gould JB 2004). Examples of secondary datasets that have been used to evaluate quality of neonatal care are the hospital discharge database and the files that link birth certificates and death certificates.

One of the required standards for hospitals involved in neonatal intensive care is that they collect data to measure their workloads and short-term outcomes (British Association of Perinatal Medicine 2001). Pooling data would allow comparison of outcomes between similar units as well as give larger numbers for a meaningful analysis of the links between perinatal care and outcome. Nevertheless, comparison of data will only be meaningful if the same denominators and standardised definitions are used and the outcomes are adjusted for differences in case mix. Quality improvement activities for any given hospital are greatly facilitated by participating in a network. The networks

facilitate vital comparisons by standardising data definition and collection standards and their reports allow confidential risk-adjusted comparisons to peer-institutions. Several NICU networks have been formed to evaluate the effectiveness and efficiency of neonatal intensive care and facilitate the use of data for quality improvement. Examples include the Vermont Oxford Network, which was established in 1988 and now includes more than 950 hospitals around the world, the Australian and New Zealand Neonatal Network, EuroNeoNet, and many others (Horbar and Gould 2006).

Nowadays, there is a general agreement for the need of mandatory national or regional perinatal-neonatal datasets for VPT babies. Pooled population data can be used for comparison of outcomes with other countries and health-care systems. National registers for VPT infants were established for example in 1994 in Portugal (VLB Infants National Registry Group 2002) and in 2004 in Finland (Finnish Medical Birth Register).

Long-term outcome data

The optimum time to measure the health status of VPT children will depend on the reason for the assessment. It is generally agreed that 2 years, corrected for GA at birth, is the best time for initial follow-up data to be collected (Marlow 2004, Lyon 2007), since at this age:

- the findings are still likely to be relevant to current clinical practice;
- the most serious neurological and sensory disability is likely to be identified, whereas at younger ages, it is believed that the diagnosis of disabling CP may not be accurate (Nelson and Ellenberg 1982) and the subject of transient neuroimpairment around 12 months of age has been well described (Bracewell and Marlow 2002);
- the effects of social and demographic factors will be minimised; and
- it should still be relatively easy to achieve a good follow-up rate.

Nowadays, there is a requirement that hospitals involved in neonatal intensive care develop and run a system for follow-up of all VPT babies who have been under their care (British Association of Perinatal Medicine 2001).

5. AIMS OF THE RESEARCH

The general objective of this research was to describe the short-term and long-term outcome for VLGA infants born in Estonia.

The specific objectives were as follows:

1. To identify the birth rate and short-term outcome (admittance to intensive care, mortality, neonatal morbidity, care, length of hospital stay, and centre differences) for VLGA infants born in Estonia in 2007–2008 (Study I) and to compare the data with that from VLGA infants born in 2002–2003 (Study II).
2. To assess the outcome at 2 years of CA with respect to attained growth and both neurosensory and developmental impairment in a national cohort of VLGA infants born in 2007 and to compare the data with that from FT control infants (Study III).
3. To establish the rate and characteristics of acute respiratory morbidity during the first two years of life in a national cohort of VLGA infants born in 2007 and, again, to compare the data with that from FT control infants (Study IV).
4. To analyse the risk factors associated with the adverse outcomes (death until hospital discharge and the presence of growth failure, CP, cognitive delay, language delay, and NDI at 2 years of CA) in VLGA infants (Study II, III).
5. To analyse the risk factors associated with the adverse outcomes of RI (wheezing, recurrent wheezing (RW), hospitalisation, and antibiotic consumption) during the first two years of life in VLGA and FT infants (Study IV).
6. Altogether, to benchmark the quality of perinatal and neonatal services in Estonia and to identify key areas for ongoing national quality improvement initiatives.

6. PATIENTS AND METHODS

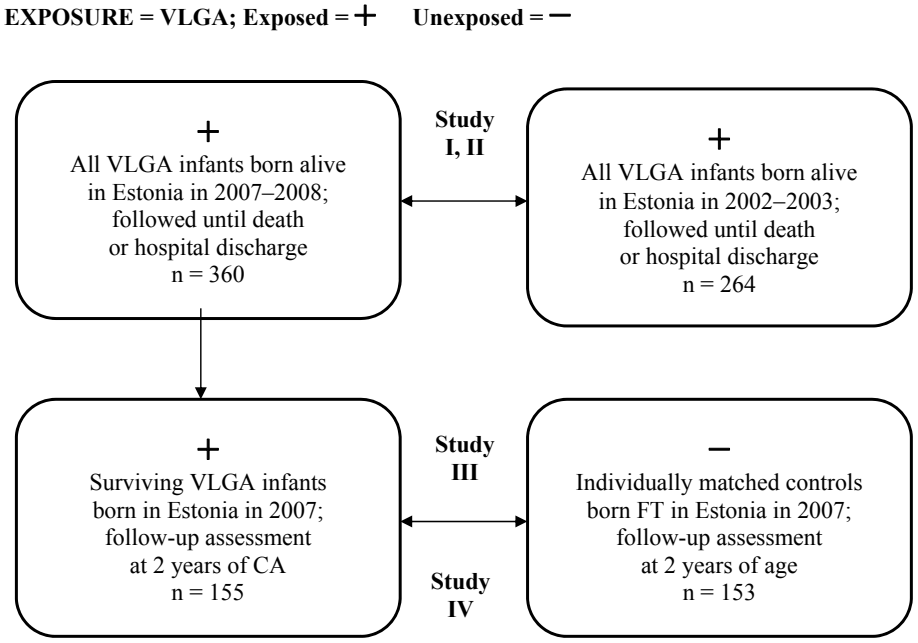
6.1. Study design, study populations, and control cohorts

This general population-based nationwide prospective cohort study of VLGA infants comprised all live-born infants in Estonia over a two-year study period 2007–2008 (Study I). The cohort of 2007–2008 was compared with a historical cohort of 2002–2003 of live-born VLGA infants for the changes in care and short-term outcome after introduction of modern perinatal and neonatal care in Estonia (Study II). A sub-cohort of VLGA infants born in 2007 was selected for additional evaluation to study 2-year outcome in regard of attained growth, neurosensory and developmental impairment (Study III), and acute respiratory morbidity (Study IV). Studies III and IV also compared the data from VLGA infants with that from individually matched FT control infants. Figure 5 outlines the study design, defines study populations, and describes registered outcome measures.

All 360 live-born infants with a GA 22^{+0} to 31^{+6} GW born in Estonia from the 1st of January 2007 to the 31st of December 2008 or from the 1st of January 2002 to the 31st of December 2003 were eligible for the short-term outcome studies (Studies I and II). Data were collected until death or discharge home, except for ROP, which was monitored until the complete vascularisation of the retina had occurred.

Figure 6 outlines the flow chart of Studies III and IV. The national study cohort consisted of all 187 live-born infants with a GA 22^{+0} to 31^{+6} GW who were born in Estonia from the 1st of January 2007 to the 31st of December 2007. Of that group, 158 (84.5%) infants survived until discharge from hospital. In addition, two children died before the follow-up examination (one as a consequence of severe chronic lung disease and the other as a consequence of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency). One infant (reported to be healthy at the standard time of the follow-up examination by a phone interview) had moved abroad. VLGA infants with congenital anomalies were included in the analyses of the studies. In total, 155 infants, 99% of those alive at the CA of 2 years, underwent an assessment at that age.

For each surviving VLGA infant, two matched FT (born at ≥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 or refused to participate, the second control was approached. In two cases, both families of identified FT control infants refused to participate in the follow-up. FT infants with a congenital disease diagnosed after the first week of life were included in the analyses of the studies. A total of 153 FT infants were enrolled in the study.



Main outcome variables registered:

Study I, II	**Study III**	**Study IV**
Admittance to care	Mortality	RI
Mortality	Growth	Wheezing
Neonatal morbidity	Neurological assessment	RW
Interventions	(PSOM, GFMCS)	Hospitalisations
Length of hospital stay	Ophthalmological assessment	Antibiotic consumption
Centre differences	Hearing assessment	
	BSID-III	
	(composite scores for	
	cognitive, language, and motor	
	skills)	

Figure 5. Study design

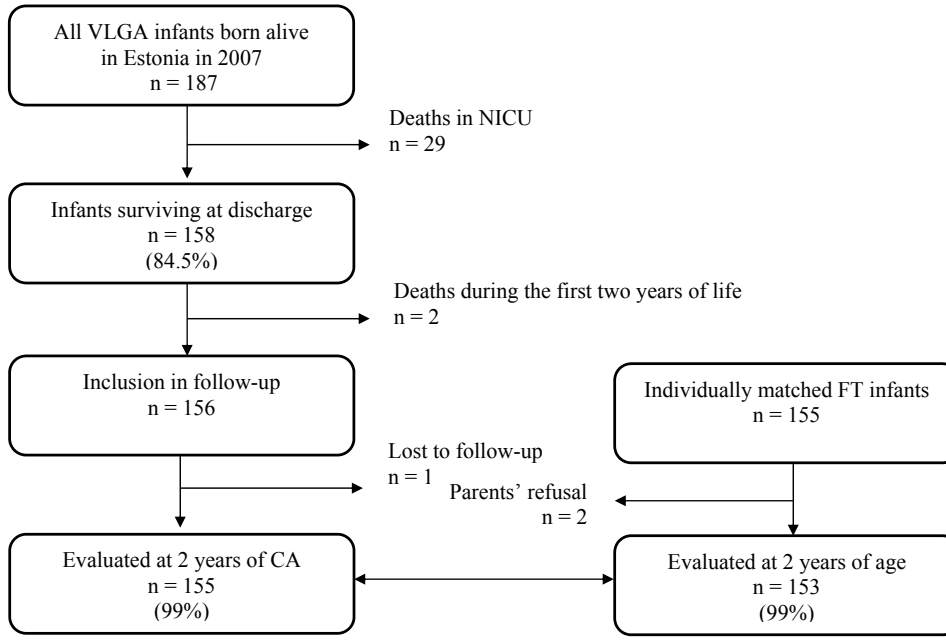


Figure 6. Flow chart of Studies III and IV

6.2. Monitoring of patients and data collection

Collection of perinatal data

In 2007–2008, all live births at <32 GW in Estonia were recorded prospectively in a national neonatal research register. The register included 68 variables that were related to pregnancy risk factors, delivery, infant condition at birth, mortality, short-term morbidity, selected neonatal procedures, and length of hospital stay. For this study, discrepancies in the data were rechecked and missing data were added from the patient records of each hospital. For the VLGA births in 2002–2003, the same 68 variables were collected retrospectively from hospital records. The Estonian Medical Birth Registry was used to obtain the number of births and the number of VPT stillbirths, and to verify that all live-born VLGA infants were accounted for.

Two-year follow-up assessment and parental interviews

When the infants reached the CA of 24 (±1) months, the families were invited to one of two centres (Tallinn Children's Hospital and Children's Clinic of Tartu University Hospital) for a physical assessment by a paediatrician, a neurological examination by a child neurologist, and an assessment of development by a clinical child psychologist, using the BSID-III (Bayley 2006). The BSID-III provides age-standardised composite scores for cognitive, language, and motor skills with a mean score of 100 (standard deviation, SD, ±15) and subtest scores

for receptive communication, expressive communication, and fine motor and gross motor skills with a mean (SD) score of 10 (±3).

In the neurological and developmental examination the PSOM (Paediatric Stroke Outcome Measure) was used by a neurologist. The PSOM measures neurological deficit and function across 5 subscales: right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive/ behaviour yielding a final 10-point deficit score (de Veber et al. 2000).

In infants with CP, the GMFCS (Palisano et al. 1997) was used to quantify motor function as follows:

1) Level 1, infants move in and out of sitting and floor sitting with both hands free to manipulate objects; infants crawl on hands and knees, pull to a stand and take steps holding on to furniture; infants walk between 18 months and 2 years of age without the need for any assistive mobility device;
2) Level 2, infants maintain floor sitting but may need to use their hands for support to maintain balance; infants creep on their stomach or crawl on hands and knees; infants may pull to a stand and take steps holding on to furniture;
3) Level 3, infants maintain floor sitting when the low back is supported; infants roll and creep forward on their stomachs;
4) Level 4, infants have head control but trunk support is required for floor sitting; infants can roll to supine and may roll to prone; and
5) Level 5, physical impairments limit voluntary control of movement; infants are unable to maintain antigravity head and trunk postures in prone and sitting; infants require adult assistance to roll.

Bodyweight, length, and head circumference were measured using routine methods. The results were related to the Estonian age- and gender-specific growth standards for 0–2 years (Kirss and Õun 2000) at time point of 2 years and were transformed into z-scores standardised for gender and age. The FT control group was representative of the general Estonian population of 2-year-old children. The data from ophthalmological and hearing assessments were derived from the national follow-up programme. Hearing was assessed by otoacoustic emission and/or brainstem auditory evoked potential measurement.

In addition, 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, infant′s age at day care attendance) as well as the presence of RI during the first two years of life were recorded. The parents or legal guardians were specifically asked about the infant's overall morbidity, the presence of acute respiratory symptoms, wheezing 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.

The examiners were aware of the birth status of the infants (premature vs. FT).

Definitions for short-term outcome and the organisation of perinatal care in Estonia

Since the re-establishment of the Estonian Republic in 1991, Estonia has reformed its healthcare system successfully. Health insurance coverage has been extended to all children and pregnant women, which ensures equality of access to health services.

Since 1992, all births in Estonia have been registered in the Estonian Medical Birth Registry without changes in the definitions or in the procedures of notification (National Institute for Health Development 2014). The definition of live birth of the World Health Organization is used (World Health Organization 1993). A newborn infant with a BW of at least 500 g carried to the 22nd completed week of pregnancy, and with no characteristics of life is considered to be stillborn. GA is based on the best obstetrical assessment, using information from ultrasound measurements and the date of the last menstrual period. In Estonia, early ultrasound examination is done to confirm pregnancy and determine GA at 8 to 12 GW. At 19 to 21 GW a second ultrasound examination is performed to screen for congenital anomalies and developmental problems. The policy is not to terminate pregnancies with antenatally recognised major congenital anomalies beyond 22 GW.

Since the 1990s, Estonia has had a regionalised system of perinatal care: three tertiary level maternity hospitals that are located in the two major cities coordinate the care of high-risk pregnancies, including preterm births at <34 GW. These maternity hospitals provide nasal CPAP but no endotracheal ventilation. All newborns requiring the highest level intensive care are transported by a specialised paediatric intensive care team to one of the paediatric intensive care units of the two regional children's hospitals, which are located at a distance of up to 6 km from the tertiary level maternity hospitals and provide full intensive care, including long-term MV and neonatal surgery. Thus, all VLGA infants in our study who required intensive care with MV must be classified as outborn. VLGA infants not requiring MV are transported to one of the neonatal intermediate care units of the regional children's hospitals.

As a rule, during the study periods, all newborn infants who were born from 22 GW onwards were resuscitated actively at birth by the attendant paediatricians or by the specialised paediatric intensive care team. Until 2014, there is no national consensus on the management of ELGA infants born at the limit of viability. However, in cases of medical futility of treatment, care is generally withdrawn.

In the present studies, the rate of regionalisation was defined as the proportion of the VLGA infants born at the tertiary level maternity hospitals as well as the proportion of infants who were admitted to care and were cared for at these hospitals longer than 48 hours. Mothers were considered to have received antenatal corticosteroids if they received 1–2 doses of dexamethasone or betamethasone. Antenatal antibiotic treatment was defined as any antibiotic drug that was administered to the mother during delivery. Infants whose BW was below the 10th percentile for their GA, according to the Fenton Intrauterine

Growth Curves, were defined as small for GA (SGA) (Fenton 2003). BPD was diagnosed if there was oxygen dependency at 36 weeks' PMA corresponding with moderate or severe BPD (Jobe and Bancalari 2001). NEC was divided into the stages defined by Bell et al. (Bell et al. 1978), PVL was defined in accordance with data from de Vries et al. (de Vries et al. 1992), and PIVH was classified according to Papile et al. (Papile et al. 1978). Brain injury (PVL and/or PIVH) was reported if diagnosed at a post-mortem examination or by routine cranial ultrasound scanning, with the last scan performed before hospital discharge. "Severe cerebral lesion" was defined as PIVH grade 3–4 and/or PVL grade 2–4 upon neonatal cranial ultrasound scanning. Sepsis was defined as clinical signs of infection with a positive blood culture. The presence of ROP was reported using the International Classification for Retinopathy of Prematurity (Committee for the Classification of Retinopathy of Prematurity 1984). Ophthalmological screening for ROP began during the fifth postnatal week and continued weekly or biweekly until the retina was completely vascularised or ROP had regressed. Survival without morbidity was defined by the absence of BPD, PIVH grade 3–4, PVL grade 2–4, ROP stage ≥3 with laser therapy, NEC stage ≥2, and⁄or blood culture-positive sepsis.

Definitions for long-term outcome at 2 years of corrected age

Infants, whose weight was below the 10th percentile according to the Estonian 0–2 year age- and gender-specific growth curves, were defined as infants with growth failure at the CA of 2 years. CP was defined and classified in accordance with the guidelines of the Surveillance of Cerebral Palsy in Europe collaborative group (Surveillance of cerebral palsy in Europe 2000). Cognitive and language delay were categorised as severe, moderate, and mild using conventional SD-banded classification of standardised scores according to the BSID-III (Bayley 2006): severe <–3 SD, moderate <–2 SD to –3 SD, and mild <–1 SD to –2 SD, respectively. Infants who functioned below the lower limit of the test were included with a score of –4 SD. Although the BSID-III has not been validated in Estonia, the original norms of the BSID-III were used and the scores for VLGA and FT control infants were compared. Developmental delay among VLGA infants was calculated according to the BSID-III original norms as well as to the FT control infants' distribution.

According to the PSOM (de Veber et al. 2000), each domain subscale (Sensorimotor Deficit, Language Deficit – Production, Language Deficit – Comprehensive, and Cognitive Deficit) was scored as 0 = no deficit, 0.5 = mild deficit, normal function, 1 = moderate deficit, slow function, or 2 = severe deficit, missing function.

The severity of neurodevelopmental impairment was defined as follows (British Association of Perinatal Medicine 2008):

1) normal development (no impairment detected in motor, cognitive, speech, hearing, and ophthalmological assessments);

2) mild neurodevelopmental disability (CP with GMFCS level 1; Cognitive and/or Language Composite Scores 1 SD to 2 SD below norm; near normal vision and hearing);
3) moderate neurodevelopmental disability (CP with GMFCS level 2; Cognitive and/or Language Composite Scores 2 SD to 3 SD below norm; hearing loss corrected with hearing aids; vision moderately reduced but better than severe visual impairment, or blind in one eye with good vision in the contralateral eye); and
4) severe neurodevelopmental disability (CP with GMFCS level 3, 4 or 5; Cognitive and/or Language Composite Score <3 SD below norm; no useful hearing even with hearing aids; blind or can only perceive light or light-reflecting objects).

Moderate and severe neurodevelopmental disabilities were taken together to represent NDI.

Weight <10th percentile, CP, Cognitive Composite Score <70, Language Composite Score <70, and NDI were defined as adverse outcomes at a CA of 2 years.

All RI cases were identified by parental reports using the following criteria: 1) episodes of illness characterised by the following symptoms (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 was 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 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 adverse 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 of breast milk received.

6.3. Statistical analysis and ethics

Statistical analysis was performed using the statistical package Stata 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Descriptive statistics for categorical variables are presented as numbers and percentages and for continuous variables as means with the SD or medians with the interquartile range (IQR). Statistical comparisons between categorical variables were performed using chi-squared or Fisher's exact test. Continuous variables were compared by Student's t-test or Mann-Whitney U-test based on the distribution of variables. Significance level of 0.05 was used. Also, OR with 95% CI were presented to describe difference in background characteristics between VLGA and FT infants.

Differences in short-term outcomes until hospital discharge between the two cohorts of VLGA infants were presented as adjusted OR with 95% CI and calculated using multiple logistic regression models. The means of the composite scores from the BSID-III were compared between different groups of infants using the mean difference and 95% CI. Multiple linear regression analysis was used to adjust the differences for the confounding variables. Associations between the characteristics of RI and maturity at birth were assessed by Poisson regression and presented as incidence rate ratios (IRR) with 95% CI or by logistic regression and presented as OR with 95% CI depending on the type of variables (count or binary variables respectively).

Simple and multiple logistic regression analyses were used to assess risk factors for the adverse outcome variables. Selected risk factors were first added in the simple model and only statistically significant risk factors ($p < 0.05$) were then included in the multiple model. The results of the multiple logistic regression analyses are presented as adjusted OR with 95% CI.

In a multiple logistic regression analysis to assess risk factors for death until discharge in Study II, both cohorts born in 2002–2003 and 2007–2008 were combined and following risk factors were tested: maternal age, complications of pregnancy (placental abruption, preeclamptic toxaemia, PPROM, chorioamnionitis), birth at a tertiary level hospital, mode of delivery, antenatal steroid and antibiotics use, infant gender, GA, BW <10th percentile, multiple birth, 1-min Apgar score <5, and major neonatal morbidities (RDS, PIVH grade 3–4, NEC, and blood culture positive sepsis).

In Study III, the following predictor variables were selected and studied in relation to the adverse outcomes (weight <10th percentile, presence of CP, Cognitive Composite Score <70, Language Composite Score <70, and NDI) at the infants' CA of 2 years: parents' education and nationality, family income and structure, complications of pregnancy (placental abruption, preeclamptic toxaemia, PPROM, chorioamnionitis), birth at a tertiary level hospital, mode of delivery, antenatal steroid use, infant gender, GA, BW <10th percentile, multiple birth, 1-min Apgar score <5, major neonatal morbidities (BPD, PIVH grade 3–4, PVL grade 2–4, NEC stage 2–3, ROP stage ≥3 with laser therapy, and positive blood culture sepsis), surfactant and postnatal steroid use, duration of MV, as well as weight <10th percentile and being fed only breast milk at hospital discharge.

In Study IV, the following risk factors for the occurrence of recurrent RI and adverse outcomes of RI (wheezing, RW, and hospitalisation) were tested:

parents' education and nationality, family income and structure, infant gender, GA, BW <10th percentile, multiple birth, BPD, duration of breastfeeding, age at day care attendance, as well as weight <10th percentile and NDI at the infants' CA of 2 years. The analysis described above in Study IV was carried out in VLGA and FT study cohorts as a whole as well as only for VLGA infants whereas the same selected risk factors were used.

The Estonian Data Inspectorate gave permission to create the national neonatal research register. The studies were approved by the Ethics Review Committee on Human Research of the University of Tartu and written informed consent for follow-up studies was obtained from all the parent(s) or legal guardian(s).

7. RESULTS AND DISCUSSION

7.1. Changes in care and short-term outcome for very low gestational age infants in Estonia

In Estonia, 360 VLGA infants were born alive in 2007–2008 and 264 in 2002–2003, with a rate of 11.3 and 10.2 per 1,000 live births, respectively ($p = 0.184$). The rate of VPT live births in Estonia showed no significant change between the two periods and was in the range of European countries involved in the EURO-PERISTAT Project (EURO-PERISTAT Project 2010). The number of live-born VLGA infants increased because of the growing number of births in Estonia.

7.1.1. Perinatal characteristics

The perinatal characteristics of the two cohorts of VLGA infants are summarised in Table 3. There were no significant differences between the two cohorts in terms of mean GA, BW, or the proportions of infants who were of male gender or born SGA. A significant increase in infants from multiple births was found on comparison of the two periods; in addition, the average maternal age had increased.

Regionalisation of perinatal care remained high: 87% of VLGA infants in 2002–2003 and 90% in 2007–2008 were born at tertiary level maternity hospitals. However, 45% of infants in 2002–2003 and 43% of infants in 2007–2008 were transferred postnatally to the regional children's hospitals during the first hour of life. When regionalisation was defined as the proportion of VLGA infants who were born at tertiary level hospitals and were cared for at these hospitals longer than 48 hours, the rate of regionalisation decreased to 23% in 2002–2003 and 27% in 2007–2008 ($p = 0.243$). The median age at the postnatal transfer for all VLGA infants was 1.2 hours in 2002–2003 and 1.4 hours in 2007–2008.

Positive trends in perinatal management were especially noticeable in more mature VLGA infants, born at 26–31 GW. This improvement was shown by a higher frequency of treatment with antenatal corticosteroids and maternal antibiotics, more births by caesarean section, and a lower proportion of babies with a 1-min Apgar score <5 in 2007–2008 than in 2002–2003. Similarly, rates of antenatal steroid use increased from 2000 to 2009 up to 77% in the management of infants with 500–1500 g BW in a study with prospectively collected register data from the Vermont Oxford Network (Soll et al. 2013). However, antenatal corticosteroid use in Europe (Rüegger et al. 2012), Canada (Shah et al. 2012), and Australia (Evans et al. 2007) still exceed rates reported by the Vermont Oxford centres in 2009 and by the present study in 2007–2008 in Estonia. Although the optimal mode of birth for VLGA infants is controversial, we found an increasing rate of caesarean delivery in the present study (42% in 2002–2003 vs. 54% in 2007–2008). Higher rates, up to 72% of caesarean section for 500–1500 g BW infants, have been reported from the United States (Soll et al. 2013).

Table 3 Perinatal characteristics for live-born VLGA infants born in Estonia in 2002–2003 and 2007–2008

	22–25 GW			**26–31 GW**			**22–31 GW**		
	2002–2003 (n = 45)	**2007–2008** (n = 72)	**p value**	**2002–2003** (n = 219)	**2007–2008** (n = 288)	**p value**	**2002–2003** (n = 264)	**2007–2008** (n = 360)	**p value**
GA, weeks, mean ± SD	24.0 ± 1.0	24.1 ± 0.9	0.647	29.0 ± 1.7	29.1 ± 1.7	0.766	28.2 ± 2.5	28.1 ± 2.5	0.641
BW, g, mean ± SD	720 ± 127	694 ± 116	0.258	1339 ± 353	1354 ± 364	0.629	1233 ± 400	1222 ± 423	0.743
Maternal age, years, mean ± SD	28.3 ± 5.0	31.0 ± 6.1	**0.014**	27.6 ± 6.4	29.2 ± 6.6	**0.007**	27.7 ± 6.2	29.5 ± 6.5	**<0.001**
Complications of pregnancy									
Placental abruption	7 (16)	6 (8)	0.227	37 (17)	26 (9)	**0.008**	44 (17)	32 (9)	**0.003**
Preeclamptic toxaemia	3 (7)	2 (3)	0.371	33 (15)	48 (17)	0.627	36 (14)	50 (14)	0.928
PPROM (≥168 h)*	16 (41)	27 (38)	0.839	66 (33)	92 (32)	0.844	82 (34)	119 (33)	0.791
Chorioamnionitis	25 (56)	37 (51)	0.706	62 (28)	66 (23)	0.180	87 (33)	103 (29)	0.253
Birth in tertiary level centre	40 (89)	66 (92)	0.616	190 (87)	258 (90)	0.326	230 (87)	324 (90)	0.261
Antenatal corticosteroids	39 (87)	56 (78)	0.331	154 (70)	236 (82)	**0.003**	193 (73)	292 (81)	**0.020**
Antenatal antibiotics	23 (51)	48 (67)	0.120	75 (34)	151 (52)	**<0.001**	98 (37)	199 (55)	**<0.001**
Caesarean section	7 (16)	15 (21)	0.628	105 (48)	180 (63)	**0.001**	112 (42)	195 (54)	**0.005**
SGA	3 (7)	9 (13)	0.366	23 (11)	19 (7)	0.114	26 (10)	28 (8)	0.389
Male gender	27 (60)	37 (51)	0.446	119 (54)	155 (54)	0.928	146 (55)	192 (53)	0.684
Multiple birth	4 (9)	15 (21)	0.122	38 (17)	86 (30)	**0.001**	42 (16)	101 (28)	**<0.001**
1-min Apgar score <5**	29 (64)	44 (62)	0.845	61 (28)	54 (19)	**0.018**	90 (35)	98 (28)	0.076

Data are shown in numbers (percentages) unless otherwise indicated.

*Unknown in four cases in 2002–2003 and in six cases in 2007–2008.

**Unknown in 25 cases in 2002–2003.

Definitions: antenatal treatment with steroids defined as 1–2 doses of dexamethasone or betamethasone; antenatal antibiotic treatment defined as any antibiotic drug administered to the mother during delivery; SGA defined as a BW below the 10^{th} percentile according to the Fenton Intrauterine Growth Curves.

7.1.2. Admittance for care and survival

Tables 4 and 5 summarise the principal data of the results. A significantly higher proportion of infants born at 22–25 GW were admitted for care in 2007–2008 than in 2002–2003. The survival rate until discharge increased significantly from 78% in 2002–2003 to 85% in 2007–2008 ($p = 0.041$) if live-born VLGA infants were included in the denominator. The lower limit of viability, defined as the lowest GA with a survival rate of over 50%, was 25 GW in both cohorts, although it should be noted, that 48% of infants born at 24 GW survived until discharge in 2007–2008 (Table 5).

The median age at death for live-born VLGA infants was 1.7 (IQR 0.1–9.5) days in 2002–2003 and 3.6 (IQR 0.6–9.3) days in 2007–2008 ($p = 0.183$). There were no significant differences detected in the proportions of infants who died in the early neonatal (16% in 2002–2003 vs. 11% in 2007–2008; $p = 0.065$), late neonatal (4 vs. 3%, respectively; $p = 0.457$) or post-neonatal periods (2 vs. 1%, respectively; $p = 0.586$). Of infants who were admitted for intensive care and died, a decision had been made to withdraw treatment in 14 and 31% of cases ($p = 0.080$), respectively.

However, it is crucial to account as well as for stillbirths and late terminations of pregnancy when comparing VPT births internationally (Evans and Levene 2001). In Estonia, the policy is not to terminate pregnancies with antenatally recognised, major congenital anomalies beyond 22 GW. The survival rate until discharge increased from 69% in 2002–2003 to 75% in 2007–2008 ($p = 0.087$) if stillborn and live-born VLGA infants were included in the denominator. According to the Estonian Abortion Registry (National Institute for Health Development 2014), only three pregnancies were ended at 22–23 GW during this period. The MOSAIC study from 10 European regions reported higher rates (0.9–21.5%) for the termination of pregnancies among the cohort of pregnancies that ended at 22–31 GW, for which only 48–74% of births were discharged from hospital alive (Draper et al. 2009).

Survival rates of VLGA infants achieved in the later cohort in Estonia are good when compared to similar population-based and multicentre studies shown in Tables 6 and 7.

In the multiple analysis to determine the risk factors for death, death was affected by GA (OR 0.66; 95% CI 0.57–0.75), 1-min Apgar score <5 (2.67; 1.49–4.79), and PIVH grade 3–4 (8.79; 4.71–16.42).

7.1.3. Neonatal morbidity

The incidence of major neonatal morbidities was not significantly different between the two studied cohorts, except for a decrease in PIVH grade 3–4 in the cohort born in 2007–2008 (Table 8). Reported morbidity rates for VPT infants between different countries, presented in Table 6 for VLGA/VLBW infants and in Table 7 for ELGA/ELBW infants, vary considerably because of differences in criteria for selection, which makes direct comparison difficult. Nevertheless,

Table 4. Admission to intensive care, survival, and morbidity-free survival of VLGA infants born in Estonia in 2002–2003 and 2007–2008

	22–25 GW		p	26–31 GW		p	22–31 GW		p
	2002–2003	2007–2008	value	2002–2003	2007–2008	value	2002–2003	2007–2008	value
All births	55	87		244	319		299	406	
Live births	45	72		219	288		264	360	
Admission to intensive care	34 (62/76)	69 (79/96)	**0.003**	214 (88/98)	284 (89/99)	0.510	248 (83/94)	353 (87/98)	**0.013**
Survival until discharge	14 (25/31)	37 (43/51)	0.050	192 (79/88)	268 (84/93)	0.055	206 (69/78)	305 (75/85)	**0.041**
Morbidity-free survival until discharge	0 (0/0)	2 (2/3)	0.520	111 (45/51)	155 (49/54)	0.542	111 (37/42)	157 (39/44)	0.758

Data are shown in numbers (percentages of all births/percentages of live births); p values were calculated to compare percentages of live births.
Definitions: morbidity-free survival defined as no supplemental oxygen required at ≥36 weeks' PMA, absence of PIVH grade 3–4, PVL grade 2–4, ROP stage ≥3 with laser therapy, NEC stage ≥2, and/or blood culture-positive sepsis.

Table 5. Admission to intensive care, survival, and morbidity-free survival by GA of VLGA infants born in Estonia

GW	Year of birth	All births (n)	Live births (n)	Admittance to intensive care	p value	Survival until discharge	p value	Morbidity-free survival until discharge	p value
22–31	**2002–2003**	**299**	**264**	**248 (94)**		**206 (78)**		**111 (42)**	0.758
	2007–2008	**406**	**360**	**353 (98)**	**0.013**	**305 (85)**	**0.041**	**157 (44)**	
22–25	**2007–2008**	**55**	**45**	**34 (76)**		**14 (31)**		**0 (0)**	
	2007–2008	**87**	**72**	**69 (96)**	**0.003**	**37 (51)**	0.050	**2 (3)**	0.520
22	2002–2003	4	3	0 (0)		0 (0)		0 (0)	
	2007–2008	4	4	3 (75)		2 (50)		0 (0)	
23	2002–2003	14	10	7 (70)		2 (20)		0 (0)	
	2007–2008	16	13	12 (92)		5 (38)		0 (0)	
24	2002–2003	16	14	11 (79)		2 (14)		0 (0)	
	2007–2008	32	25	24 (96)		12 (48)		1 (4)	
25	2002–2003	21	18	16 (89)		10 (56)		0 (0)	
	2007–2008	35	30	30 (100)		18 (60)		1 (3)	
26–31	**2002–2003**	**244**	**219**	**214 (98)**		**192 (88)**		**111 (51)**	
	2007–2008	**319**	**288**	**284 (99)**	0.510	**268 (93)**	0.055	**155 (54)**	0.542
26	2002–2003	32	27	26 (96)		17 (63)		3 (11)	
	2007–2008	32	28	26 (93)		23 (82)		2 (7)	
27	2002–2003	28	23	21 (91)		19 (83)		6 (26)	
	2007–2008	49	40	39 (98)		35 (88)		11 (28)	
28	2002–2003	31	29	29 (100)		25 (86)		14 (48)	
	2007–2008	43	38	38 (100)		36 (95)		15 (39)	
29	2002–2003	43	38	37 (97)		34 (89)		18 (47)	
	2007–2008	43	41	40 (98)		39 (95)		25 (61)	
30	2002–2003	49	45	44 (98)		42 (93)		28 (62)	
	2007–2008	68	63	63 (100)		59 (94)		37 (59)	
31	2002–2003	61	57	57 (100)		55 (96)		42 (74)	
	2007–2008	84	78	78 (100)		76 (97)		65 (83)	

Data are shown in numbers (percentages of live births) unless otherwise indicated.

Definitions: morbidity-free survival defined as no supplemental oxygen required at ≥36 weeks' PMA, absence of PIVH grade 3–4, PVL grade 2–4, ROP stage ≥3 with laser therapy, NEC stage ≥2, and/or blood culture positive sepsis.

Table 6. Comparison of mortality and selected morbidity in VLGA and VLBW infants in various geographical or multicentre cohorts

Author (year) Country	Cohort	Definitions	Birth years	LB or A	Survival to discharge	PIVH (grade 3-4)	BPD	NEC (stage 2–3)	ROP (stage ≥3) or ROP treatment	Sepsis
		(GA or BW)		(n)	(%)	(%)	(%)	(%)	(%)	(%)
Darlow et al. (2003) Australia	PB	<1500 g	1986	413 (A)	82 (of A)	4 (of E)	23 (of S at 36 PMA)	NA	4 (of E)	NA
			1998–1999	1084 (A)	90 (of A)	2 (of E) (PIVH grade 4)	16 (of S at 36 PMA)	NA		NA
Zeitlin et al. (2010) France	PB	24–31 GW	1997	488 (LB)	81 (of LB)	11	14 (of A)	NA	NA	NA
			2003	580 (LB)	85 (of LB)	4	15 (of A)	NA	NA	NA
Kusuda et al. (2006) Japan	MC	≤1500 g	2003	2145 (A)	89 (of A)	7 (of E)	28 (of A)	4 (of A) (NEC + IP)	19 (of A)	8 (of A)
Bode et al. (2009) USA	PB	<30 GW	1985–1986	138 (LB)	82 (of LB)	10 (of S)	35 (of S)	4 (of S)		23 (of S)
			2005–2006	187 (LB)	93 (of LB)	5 (of S)	56 (of S)	2 (of S)		26 (of S)
Murphy et al. (2010) Ireland	MC	<1500 g	2004	716 (A)	81 (of A)	11 (of A)	19 (of A)	NA	NA	26 (of A)
			2005	718 (A)	82 (of A)	10 (of A)	19 (of A)	NA	NA	26 (of A)
			2006	659 (A)	85 (of A)	10 (of A)	21 (of A)	NA	NA	25 (of A)
			2007	796 (A)	85 (of A)	5 (of A)	15 (of A)	NA	NA	25 (of A)
Rüegger et al. (2012) Switzerland	PB	<32 GW and/or <1500 g	1996	3090 (LB)	87 (of LB)	6 (of A)	18 (of A)	3 (of A)	2 (of A)	9 (of A)
			2000		84 (of LB)	7 (of A)	14 (of A)	3 (of A)	1 (of A)	11 (of A)
			2004		87 (of LB)	7 (of A)	17 (of A)	2 (of A)	1 (of A)	9 (of A)
			2008		88 (of LB)	4 (of A)	15 (of A)	2 (of A)	2 (of A)	11 (of A)
Toome et al. (2012) Estonia	PB	22–31 GW	2002–2003	264 (LB)	78 (of LB)	15 (of A) 9 (of S)	20 (of S)	7 (of A)	11 (of S)	23 (of A)
			2007–2008	360 (LB)	85 (of LB)	12 (of A) 5 (of S)	24 (of S)	12 (of A)	12 (of S)	22 (of A)

Abbreviations: A indicates admissions; E, examinations; IP, intestinal perforation; LB, live births; MC, multicentre; NA, data not available; PB, population-based; S, survivors at discharge unless otherwise stated.
Definitions: BPD defined as oxygen dependency at 36 weeks' PMA.

Table 7. Comparison of mortality and selected morbidity in ELGA and ELBW infants in various geographical or multicentre cohorts

Author (year) Country	Cohort	Definitions (GA or BW)	Birth years	LB or A (n)	Survival to discharge (%)	PIVH (grade 3-4) (%)	BPD (%)	NEC (stage 2–3) (%)	ROP (stage ≥3) or ROP treatment (%)	Sepsis (%)
Costeloe et al. (2000) UK and Ireland	PB	<26 GW	1995	811 (A)	39 (of A)	NA	74 (of S)	NA	15 (of S)	NA
Tommiska et al. (2007) Finland	PB	<1000 g	1996–1997 1999–2000	351 (LB) 339 (LB)	60 (of LB) 65 (of LB)	16 (of A) 17 (of A)	39 (of S) 49 (of S)	8 (of A) 4 (of A) (NEC + IP)	9 (of S) 5 (of S)	23 (of A) 31 (of A)
Vanhaesebrouck et al. (2004) Belgium	PB	22–26 GW	1999–2000	322 (LB)	54 (of LB)	25 (of A) 12 (of S)	45 (of S)	16 (of S) (Surgical NEC + IP)	20 (of S)	NA
Markestad et al. (2005) Norway	PB	22–27 GW or 500–999 g	1999–2000	462 (A)	81 (of A)	6 (of S)	33 (of S)	5 (of S)	4 (of S)	NA
Fischer et al. (2009) Switzerland	PB	22–25 GW	2000–2001 2003–2004	220 (LB) 204 (LB)	31 (of LB) 40 (of LB)	2 (of S) 4 (of S)	24 (of S) 33 (of S)	NA	8 (of S) 11 (of S)	NA
Stoll et al. (2010) USA	MC	22–28 GW and 401–1500 g	2003–2007	9575 (LB)	72 (of LB)	16 (of E)	42 (of S at 36 PMA)	11 (of S >12 h)	16 (of E)	36 (of S >3 days)
The Express Group (2010) Sweden	PB	22–27 GW	2004–2007	638 (A)	78 (of A)	10 (of S at 1 year)	73 (of S at 1 year)	6 (of S at 1 year)	34 (of S at 1 year)	41 (of S at 1 year)
de Waal et al. (2012) Netherlands	PB	23–27 GW	2007	276 (LB)	52 (of LB)	7 (of S)	24 (of S)	9 (of S)	8 (of S)	NA
Toome et al. (2012) Estonia	PB	22–25 GW	2002–2003	45 (LB)	31 (of LB)	35 (of A) 36 (of S)	50 (of S)	6 (of A)	64 (of S)	26 (of A)
			2007–2008	72 (LB)	51 (of LB)	35 (of A) 8 (of S)	62 (of S)	11 (of A)	51 (of S)	38 (of A)

Abbreviations: A indicates admissions; E, examinations; IP, intestinal perforation; LB, live births; MC, multicentre; NA, data not available; PB, population-based; S, survivors at discharge unless otherwise stated.
Definitions: BPD defined as oxygen dependency at 36 weeks' PMA.

Table 8. In-hospital death and major neonatal morbidity for VLGA infants admitted for care, born in Estonia in 2002–2003 and 2007–2008

	22–25 GW			26–31 GW			22–31 GW			
	2002–2003 (n = 34)	**2007–2008** (n = 69)	**p value**	**2002–2003** (n = 214)	**2007–2008** (n = 284)	**p value**	**2002–2003** (n = 248)	**2007–2008** (n = 353)	**p value**	**Adjusted OR (95% CI)****
In-hospital death	20 (59)	32 (46)	0.296	22 (10)	16 (6)	0.061	42 (17)	48 (14)	0.296	**0.51 (0.29–0.89)**
PIVH grade 3–4	12 (35)	24 (35)	0.959	25 (12)	18 (6)	0.052	37 (15)	42 (12)	0.327	**0.55 (0.31–0.98)**
NEC stage ≥2	2 (6)	8 (12)	0.491	16 (7)	35 (12)	0.100	18 (7)	43 (12)	0.055	1.76 (0.96–3.24)
Positive blood culture sepsis >72 h	9 (26)	26 (38)	0.279	49 (23)	51 (18)	0.177	58 (23)	77 (22)	0.692	0.86 (0.57–1.32)
BPD*	7 (50)	23 (62)	0.529	35 (18)	50 (19)	0.999	42 (20)	73 (24)	0.388	1.25 (0.74–2.09)
PIVH grade 3–4*	5 (36)	3 (8)	**0.028**	13 (7)	11 (4)	0.205	18 (9)	14 (5)	0.058	**0.42 (0.19–0.98)**
PVL grade 2–4*	0 (0)	1 (3)	0.999	15 (8)	10 (4)	0.063	15 (7)	11 (4)	0.068	0.52 (0.22–1.21)
ROP stage ≥3 + laser therapy*	9 (64)	19 (51)	0.533	13 (7)	16 (6)	0.846	22 (11)	35 (11)	0.886	0.73 (0.35–1.55)

Data are shown in numbers (percentages) of infants admitted for care.

*Data are shown in numbers (percentages) of survivors.

**Adjusted for GA, gender, maternal age, antenatal steroids, antenatal antibiotics, caesarean section, multiple birth, and 1-min Apgar score; adjusted OR refers to comparison for the whole cohort.

Definitions: BPD defined as oxygen dependency at 36 weeks' PMA.

it can be concluded cautiously that, in the present study in Estonia, the incidence of major neonatal morbidities, especially the rate of severe PIVH, ROP, and NEC, was higher than in other reports (Darlow et al. 2003, Vanhaesebrouck et al. 2004, Markestad et al. 2005, Tommiska et al. 2007, Fischer et al. 2009, EXPRESS 2010, Murphy et al. 2010, Zeitlin et al. 2010a).

Morbidity-free survival did not increase significantly over time. Overall, 44% of VLGA infants who were born in 2007–2008 survived until discharge without major, early morbidities, whereas only two infants born at 22–25 GWs were free of them. It was 29 completed GW as milestone for survival over 50% without any major morbidities at discharge (Table 5). Differences in morbidity-free survival for VLGA infants born in 2002–2003 and 2007–2008 by GA are shown in Figure 7. While survival increased between the two studied periods, morbidity-free survival remained unchanged.

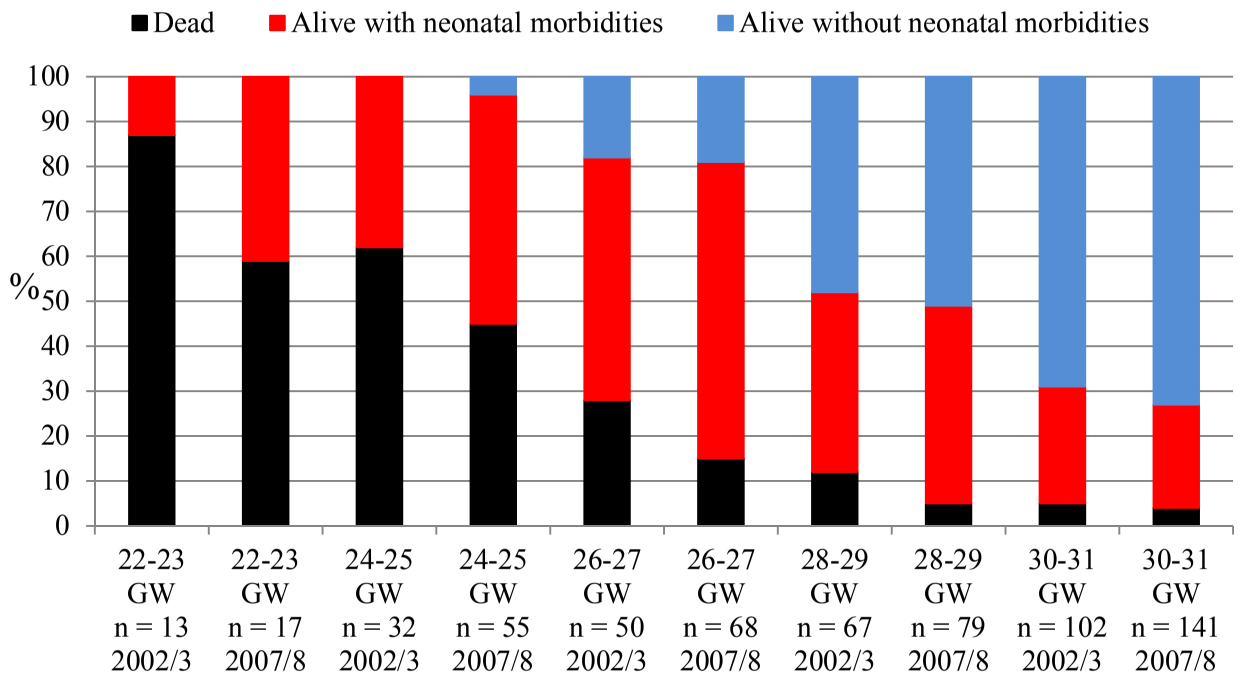
7.1.4. Neonatal interventions and length of hospital stay

In 2007–2008, the care strategies adopted were significantly less invasive (Table 9). The changes included decrease in intubation after birth, MV, inotropic therapy, and the administration of antibiotics, with the use of vancomycin almost halved. In addition, the median duration of MV and antibiotic treatment was shortened, whereas in contrast, surgical closure of PDA was used more often in 2007–2008 than in 2002–2003.

Changes in the use of both invasive and non-invasive respiratory support have been reported also in other neonatal networks. A study from the Vermont Oxford Network with prospectively collected register data for 355,806 infants born from 2000 to 2009, reported a significant increase of less-invasive methods of respiratory support, such as nasal CPAP, use of nasal ventilation, and high-flow nasal cannula (Soll et al. 2013), whereas most of the changes were observed within each of four BW strata (501–750 g, 751–1000 g, 1001–1250 g, 1251–1500 g). In southern Sweden between 1995 and 2004, Lundqvist et al. (Lundqvist et al. 2009) reported an increased use of assisted ventilation of infants <25 GW, but greater use of CPAP in infants 25 to 28 GW. In Switzerland, Rüegger et al. (Rüegger et al. 2012) reported that the use of CPAP increased from 43% in 1996 to 73% in 2008 in VPT infants.

Whereas the use of postnatal steroids reached the zenith in the late 1990s with 24% of all VLBW infants exposed in 2000 and decreased to 8% in 2009 in the United States (Soll et al. 2013), the use of postnatal steroids remained low during the both studied periods in Estonia, 4% in 2002–2003 and 5% in 2007–2008.

Improved survival rates in the later period were not associated with a longer hospital stay. The median length of hospital stay for infants who were admitted for care but died was 5 days in both cohorts ($p = 0.968$). For survivors, the median length of stay was 55 (IQR 41–77) days in 2002–2003 and 52 (IQR 37–79) days in 2007–2008 ($p = 0.379$).



Definitions: neonatal morbidities defined as supplemental oxygen required at ≥36 weeks' PMA, presence of PIVH grade 3–4, PVL grade 2–4, ROP stage ≥3 with laser therapy, NEC stage ≥2, and⁄or blood culture-positive sepsis.

Figure 7. Differences in short-term outcome at hospital discharge for VLGA infants by GA born in Estonia in 2002–2003 and 2007–2008

Table 9. Intensive care interventions for VLGA infants born in Estonia in 2002–2003 and 2007–2008

	22–25 GW			**26–31 GW**			**22–31 GW**		
	2002–2003 (n = 34)	**2007–2008** (n = 69)	**p value**	**2002–2003** (n = 214)	**2007–2008** (n = 284)	**p value**	**2002–2003** (n = 248)	**2007–2008** (n = 353)	**p value**
Endotracheal intubation during the 1st hour of life	34 (100)	62 (90)	0.092	101 (47)	86 (30)	**<0.001**	135 (54)	148 (42)	**0.002**
Surfactant therapy	28 (82)	68 (99)	**0.005**	95 (44)	136 (48)	0.439	123 (50)	204 (58)	**0.047**
MV	34 (100)	69 (100)		143 (67)	154 (54)	**0.005**	177 (71)	223 (63)	**0.036**
Duration of MV, h, median (IQR)	300 (48–672)	216 (72–768)	0.574	168 (72–432)	72 (24–168)	**<0.001**	168 (72–488)	96 (48–216)	**<0.001**
Indomethacin or ibuprofen for PDA	19 (56)	33 (48)	0.442	46 (21)	64 (23)	0.782	65 (26)	97 (27)	0.730
Surgical ligation for PDA	4 (12)	24 (35)	**0.018**	4 (2)	30 (11)	**<0.001**	8 (3)	54 (15)	**<0.001**
Infants treated at least once with antibiotics	33 (97)	69 (100)	0.330	209 (98)	262 (92)	**0.009**	242 (98)	331 (94)	**0.031**
Duration of antibiotic treatment, days, median (IQR)	21 (3–41)	12 (4–31)	0.886	19 (11–31)	8 (5–14)	**<0.001**	19 (10–33)	8 (5–16)	**<0.001**
Infants treated with vancomycin	16 (47)	31 (45)	0.838	78 (36)	41 (14)	**<0.001**	94 (38)	72 (20)	**<0.001**
Infants treated with dexamethasone*	3 (21)	9 (24)	0.999	5 (3)	7 (3)	0.999	8 (4)	16 (5)	0.529
Infants treated with inotropes	26 (76)	55 (80)	0.706	97 (45)	75 (26)	**<0.001**	123 (50)	130 (37)	**0.002**

Data are shown in numbers (percentages) of infants admitted for care unless otherwise indicated.
*Data are shown in numbers (percentages) of survivors.

7.1.5. Centre differences

When the neonatal intensive care strategies and the mortality and morbidity rates between the groups of VLGA infants born in the three tertiary level maternity hospitals were compared, some differences were found in the neonatal management during the later study period 2007–2008. The mean GA and BW as well as the proportion of infants born at <26 GW did not differ between the groups. However, the early interventions were less invasive in hospital A (Table 10). Namely, significantly higher proportion of infants born in this hospital were treated with early CPAP and a lower proportion of infants needed endotracheal intubation during the first hour of life and/or MV during the entire hospital stay. Less invasive care strategies were introduced in hospital A during the later study period 2007–2008. Among VLGA infants born in hospital A in 2007 compared with the infants born in 2008, the rate of early CPAP was 51 vs. 73% whereas the rate of intubation during the first hour of life was 41 vs. 20% and of MV until discharge 51 vs. 43%. Recently higher rates of early CPAP and lower rates of MV have been reported among ELGA infants compared with the whole Estonian study cohort (Table 9). For example, a single-centre outcome data of infants born at 23–27 GW who have been managed by a new mode of surfactant administration without intubation showed that 68% of infants stayed on CPAP on day 3 and the rate of MV was 59% during the entire hospital stay (Klebermass-Schrehof et al. 2013). From hospital A, 41% of VLGA infants were transported to the paediatric intensive care unit and 59% to the neonatal intermediate care unit whereas from hospital B and C, 95 and 87% of infants, respectively, were transported to the paediatric intensive care units. The mean age of infants at the transport was 115 hours for infants born in hospital A and four hours for infants born in hospital B and C.

Any significant differences were found in the rates of mortality and major neonatal morbidities (BPD, PIVH grade 3–4, PVL grade 2–4, NEC stage 2–3, positive blood culture sepsis >72 hours, and ROP stage ≥3 with laser therapy) between the groups of VLGA infants born in hospital A, B, or C. However, the rate of pneumothorax was the highest among infants born in Hospital A and the rate of morbidity-free survival was significantly higher among infants born in hospital A than in hospital B (Table 10). The difference in morbidity-free survival between hospital A and B remained statistically significant after adjustment for gender, BW, GA, BW $<10^{th}$ percentile, multiple birth, antenatal corticosteroid treatment, and Apgar score at birth.

Table 10. Centre differences in neonatal management and morbidity for VLGA infants born in Estonia in 2007–2008 and admitted for care

	Tertiary level maternity hospitals				
	A (n = 140)	B (n = 76)	C (n = 103)	p value	OR (95% CI)
Early CPAP	85 (61)	3 (4)	6 (6)	**<0.001***	**37.6 (11–125)**
				<0.001**	**25.0 (10–61)**
				0.735***	1.5 (0.4–6.2)
Endotracheal intubation during the 1st hour of life	45 (32)	52 (68)	42 (41)	**<0.001***	**4.6 (2.5–8.3)**
				0.165**	1.5 (0.9–2.5)
				<0.001***	**3.2 (1.7–5.9)**
Surfactant therapy	57 (41)	60 (79)	69 (67)	**<0.001***	**5.3 (2.8–10.1)**
				<0.001**	**2.4 (1.4–4.1)**
				0.023***	**2.2 (1.4–4.3)**
MV	67 (48)	60 (79)	69 (67)	**<0.001***	**4.1 (2.1–7.8)**
				0.003**	**2.2 (1.3–3.8)**
				0.078*****	1.9 (0.7–5.1)
Pneumothorax	20 (14)	6 (8)	2 (2)	0.168*	1.9 (0.7–5.1)
				0.003**	**5.6 (1.6–19.2)**
				0.172*****	2.9 (0.7–11.8)
Morbidity-free survival until discharge	62 (44)	45 (59)	53 (51)	**0.036***	**1.8 (1.0–3.2)**
				0.269**	1.3 (0.8–2.2)
				0.303*****	1.4 (0.8–2.5)

Data are shown as numbers (percentages) of infants admitted for care.
*Statistical difference between hospital A and B.
** Statistical difference between hospital A and C.
*** Statistical difference between hospital B and C.
Definitions: morbidity-free survival defined as no supplemental oxygen required at ≥36 weeks' PMA, absence of PIVH 3–4, PVL grade 2–4, ROP stage ≥3 with laser therapy, NEC stage ≥2, and/or blood culture-positive sepsis.

7.2. Long-term outcome for very low gestational age infants at 2 years of corrected age in Estonia

The follow-up studies regarding growth, neurosensory and developmental impairment (Study III), and respiratory morbidity (Study IV) at 2 years of CA, were carried out in survived VLGA infants and their FT controls born in 2007. The mean age at assessment for the VLGA group was 24.2 (SD 1.1) corrected months and for the FT control group it was 24.4 (SD 0.8) months, with a mean difference of 0.15 months (95% CI: –0.06–0.36).

The background characteristics of the final study population (155 VLGA and 153 FT infants in the control group) are summarised in Tables 11 and 12. Three VLGA infants had a congenital anomaly or a syndrome of clinical significance

Table 11. Peri- and neonatal variables of VLGA and FT infants born in Estonia in 2007

	VLGA infants (155 infants)	**FT infants** (153 infants)	**OR (95% CI)** or **p value** for comparing means
Perinatal variables			
Antenatal corticosteroids	128 (83)	0	NA
Multiple births	38 (25)	2 (1)	**24.5 (5.8–103.7)**
GA, weeks, mean (95% CI)	28.8 (28.4–29.1)	39.6 (39.4–39.7)	**<0.001**
BW, g, mean (95% CI)	1314 (1252–1377)	3611 (3536–3685)	**<0.001**
SGA	10 (6)	7 (5)	1.4 (0.5–3.9)
Male gender	88 (57)	87 (57)	1.0 (0.6–1.6)
Surfactant	88 (57)	0	NA
MV	91 (59)	0	NA
Postnatal steroids	8 (5)	0	NA
Morbidity			
PIVH grade 3–4 and/or PVL grade 2–4	15 (10)	0	NA
BPD	29 (19)	0	NA
ROP stage ≥3 with laser therapy	13 (8)	0	NA
Positive blood culture sepsis	40 (26)	0	NA
NEC stage 2–3	18 (12)	0	NA
Weight <10th percentile at discharge	85 (55)	NA	NA

Data are shown in numbers (percentages) unless otherwise indicated.
Abbreviations: NA indicates not applicable.
Definitions: BPD defined as oxygen dependency at 36 weeks' PMA; SGA defined as weight below the 10th percentile for the GA according to the Fenton Intrauterine Growth Curves.

Table 12. Demographic variables of VLGA and FT infants born in Estonia in 2007

	VLGA infants (155 infants, 134 mothers)	**FT infants** (153 infants, 152 mothers)	**OR (95% CI)** or **p value** for comparing means
Maternal age, years, mean (95% CI)	31.4 (30.3–32.5)	30.5 (29.7–31.3)	0.194
Maternal higher education	36 (27)	76 (50)	**0.4 (0.2–0.6)**
Single mother	19 (14)	15 (10)	1.5 (0.7–3.2)
Paternal age, years, mean (95% CI)	34.4 (33.2–35.7)	34.4 (32.2–36.7)	0.210
Paternal higher education	20/124 (16)	51/151(34)	**0.4 (0.2–0.7)**
Low income of the family	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, months, mean (95% CI)	22.7 (21.8–23.7)	20.4 (19.6–21.1)	**<0.001**
Day care attendance at 2 years of CA	51 (33)	63 (41)	0.7 (0.4–1.1)
Duration of breastfeeding, days, mean (95% CI)	147 (119–175)	308 (273–342)	**<0.001**

Data are shown in numbers (percentages) unless otherwise indicated.

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

(Tetralogy of Fallot, congenital laryngeal stenosis, and Hallermann-Streiff syndrome) and two FT infants had a congenital disease (toxoplasmosis and hypothyreosis) diagnosed after the first week of life. VLGA infants were more likely to be from low-income families than FT infants and their parents were less likely to have higher education. None of the VLGA infants required oxygen therapy at home. BPD was diagnosed in 29 (19%) of the VLGA infants; in 19 (49%) and 10 (9%) infants born at 22–27 and 28–31 GW, respectively. During the first year of life, 12 (8%), and during the second year seven (5%) VLGA infants were given a monthly injection of respiratory syncytial virus monoclonal antibody during peak respiratory syncytial virus season. The mean duration of partial and/or exclusive breastfeeding in VLGA infants was significantly shorter than in FT infants, 147 days (95% CI: 119–175) for VLGA and 308 days (95% CI: 273–342) for infants in the FT control group. 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.

7.2.1. Survival

The overall two-year survival rate for the VLGA infants born alive in Estonia in 2007 was 83%, whereas it was 47% for infants born at 22–25 weeks and 92% for infants born at 26–31 weeks.

The survival of ELGA and VLGA infants in Estonia during the first two years of life was higher (Wood et al. 2000, Rattihalli et al. 2011) or comparable (Rijken et al. 2003, Vohr et al. 2005b, Fily et al. 2006, De Groote et al. 2007, Munck et al. 2010) to that reported in several other population-based or multicentre studies, although higher survival rates have also been reported (Bode et al. 2009, Doyle et al. 2011, Serenius et al. 2013) (Tables 13 and 14).

7.2.2. Growth

The VLGA infants had significantly lower bodyweight, length, and smaller head circumference when compared with infants from the FT control group (Table 15). The mean difference in weight was 973 g (0.66 z-scores; 1116 g (0.76 z-scores) for boys and 787 g (0.51 z-scores) for girls). For body length, the mean difference was 1.3 cm (0.36 z-scores; 1.5 cm (0.38 z-scores) for boys and 1.2 cm (0.32 z-scores) for girls), and for head circumference it was 0.5 cm (0.25 z-scores; 0.6 cm (0.29 z-scores) for boys and 0.3 cm (0.19 z-scores) for girls). All of the z-scores were significantly different between study groups. Among all the VLGA infants, 31% were below the 10^{th} percentile by bodyweight (38% of boys and 22% of girls) of Estonian 2-year child growth chart, while 65% of them were more mature infants born at 28 to 31 GW. The comparable numbers were 23% for length (23% of boys and 22% of girls) and 21% for head circumference (22% of boys and 19% of girls).

The duration of breastfeeding was not associated with a weight of $<10^{th}$ percentile at the follow-up examination.

Of greatest concern was the finding that while 6% of VLGA infants were SGA at birth and 55% were <10th percentile of weight at discharge, at the CA age of 2 years, 31% of them (44% of infants born before 28 GW and 27% of those born at 28 to 31 GW) were still below the 10th percentile by bodyweight of Estonian 2-year child growth chart. However, previously the Neonatal Research Network of the National Institute of Child Health and Human Development had also reported that while 16% of ELBW infants were SGA at birth, by 36 weeks of PMA 89% had growth failure. Furthermore, by CA of 18 to 22 months, 40% still were at less than the 10th percentile for weight, length, and head circumference (Dusick et al. 2003).

7.2.3. Neurosensory outcomes

In the present study, no impairment with respect to neurosensory and developmental outcomes was found in 93 (60%) of VLGA infants.

Throughout the world, the condition that is associated most commonly with a VPT birth is CP. The prevalence of CP in the present study was 90.9 per 1,000 VLGA live births (17/187). For the group of survivors at the CA of 2 years, the prevalence of CP was 11% (18% for infants born at 22–25 GW and 10% for infants born at 26–31 GW). From VLGA infants with CP, 65% were born at 28 to 31 GW. Of the 17 infants who had CP, 13 (8% of VLGA infants) had a GMFCS level of 2–5. The most common type of CP was spastic diplegia (seven cases). The second most common neurological problem was hydrocephalus, which was diagnosed in eight infants (5%), five of whom had CP. One child had epilepsy and needed antiepileptic therapy.

The prevalence of CP from previously reported follow-up studies of ELGA/ELBW and VLGA/VLBW infants is shown in Tables 13 and 14.

The prevalence of severe impairments of hearing and vision among VLGA infants in the present study remained reassuringly low (Tables 13 and 14). Neonatal screening for both conditions is well established in Estonia, and laser coagulation provides good ocular results for the treatment of ROP. Although 13 infants (8%) had received laser therapy for both eyes, only one child was blind in one eye at follow-up examination. Two (1%) infants suffered from hearing impairment that necessitated hearing rehabilitation.

Table 13. Comparison of survival and impairment in young age among VLGA/VLBW infants in various cohorts

Author (year) Country	Cohort	Definitions (GA/BW)	Birth years	Live births (n)	CA at FU	Survival of LB to FU (%)	FU rate (of S) (%)	CP (%)	Blind (%)	Deaf (%)	Mean cognitive index ± SD (test)	Cognitive index <70 (<-2 SD) (%)	NDI (%)	Survival without NDI (%)
Vohr et al. (2005)	MC	27–32 GW	1993–1994	797	18–22	82 (to D)	70	12	1.4	1.4	NA	30	40	NA
			1995–1996	784	months	87 (to D)	81	11	0.4	0.4	NA	26	32	NA
USA			1997–1998	737		86 (to D)	82	11	0.4	0.4	NA	23 (BSID-II)	28	NA
Fily et al. (2006) France	PB	<32 GW	1997	634	24 months	86 (to D)	99.6	9	0.2	0.8	94 ± 11 (Brune-Lezine test)	5 (Brune-Lezine test)	NA	NA
Bode et al. 2009	PB	<31 GW	1985–1986	138	24 months	77	99	7	2	0	94 ± 22 (BSID-I)	17 (BSID-I)	19	62 (of LB)
USA			2005–2006	187		92	97	5	1	1	92 ± 13 (BSID-III)	10 (BSID-III)	9	81 (of LB)
Munck et al. (2010) Finland	PB	≤1500 g	2001–2006	261	24 months	84	83	7	0	2.2	101.7 ± 15.4 (BSID-II)	3 (BSID-II)	10	NA
Toome et al. (2013) Estonia	PB	<32 GW	2007	187	24 months	83	99.4	11	0	1.3	94.7 ± 15.4 (BSID-III)	5 (BSID-III)	12	73 (of LB)

Data are shown for CP, blindness, deafness, mean cognitive index, cognitive index <70 (<-2 SD), and NDI in survivors with a follow-up assessment.

Abbreviations: D indicates hospital discharge; FU, follow-up; LB, live births; MC, multicentre; NA, not available; PB, population-based.

Inclusion criteria, definitions: Vohr et al.: NDI defined as the presence of any of the following: moderate to severe CP, cognitive scale score <-2 SD, psychomotor scale score <-2 SD, blind in both eyes, or hearing loss requiring amplification in both ears; Fily et al.: children with congenital anomalies excluded; children unable to complete the psychological assessment test because of severe delay excluded; Bode et al.: children unable to complete the psychological assessment test because of severe delay were assigned scores of 50; NDI defined as an abnormal neurologic examination result interfering with independent ambulation, blindness, deafness, or severe developmental delay (cognitive scale score of >2 SD below the mean of the respective control group); Munck et al.: children with congenital anomalies or syndromes, of mothers self-reported use of illicit drugs or alcohol during pregnancy, and with BW <-2 SD for GA excluded; NDI defined as CP, cognitive scale score of <-2 SD, hearing loss requiring a hearing aid, or blindness; Toome et al.: children unable to complete the psychological assessment test because of severe delay were assigned scores of -4 SD; NDI defined as CP interfering with independent ambulation, cognitive or language scale score of <-2 SD, hearing loss corrected with aids or deafness, blind in at least one eye.

Table 14. Comparison of survival and impairment in young age among ELGA/ELBW infants in various cohorts

Author (year) Country	Cohort	Definitions (GA/BW)	Birth years	Live births (n)	CA at FU	Survival of LB to FU (%)	FU rate (of S) (%)	CP (%)	Blind (%)	Deaf (%)	Mean cognitive index ± SD (test)	Cognitive index <70 (<-2 SD) (%)	NDI (%)	Survival without NDI (%)
Wood et al. (2000) UK, Ireland	PB	<26 GW	1995	1185 (811 A)	30 months	26 38 (of A)	92	18	2	3	84.2 ± 12 (BSID-II)	30 (together with PDI) (BSID-II)	23	19 (of LB) 28 (of A)
Rijken et al. (2003) Netherlands	PB	23–26 GW	1996–1997	46	24 months	65	87	NA	NA	NA	NA	~18 (BSID-I)	36	43 (of LB)
Vohr et al. (2005) USA	MC	22–26 GW	1993–1994 1995–1996 1997–1998	1705 1573 1802	18–22 months	55 (to D) 56 (to D) 61 (to D)	74 84 84	20 19 18	2 2 1	3 2 2	NA	42 39 37 (BSID-II)	50 47 45	NA NA NA
De Groote et al. (2007) Belgium	PB	22–26 GW	1999–2000	169 (161 A)	36 months	46 43 (of A)	84	25	2	1	81.2 ± 18.8 (BSID-II)	29 (BSID-II)	35	37 (of LB)
Wilson-Costello et al. (2007) USA	SC	500–999 g	1982–1989	496	18–20 months	49	90	8	5	3	86.4 ± 20 (BSID-I)	20 (BSID-I)	28	33 (of LB)
			1990–1999	749		68	92	13	1	6	84.0 ± 19 (BSID-II)	24 (BSID-II)	35	43 (of LB)
			2000–2002	233		71	92	5	1	1	85.9 ± 20 (BSID-II)	21 (BSID-II)	23	53 (of LB)
Rattihalli et al. (2011) UK	PB	<26 GW	1991–1993 2001–2003	NA 347	24 months	NA 30	93 97	16 28	2 3	9 7	NA	31 (<-3 SD) 21 (<-3 SD)	34 (ACC) 39 (OMD)	NA 18 (of LB)

Author (year) Country	Cohort	Defini-tions (GA/BW)	Birth years	Live births (n)	CA at FU	Survival of LB to FU (%)	FU rate (of S) (%)	CP (%)	Blind (%)	Deaf (%)	Mean cognitive index ± SD (test)	Cognitive index <70 (<-2 SD) (%)	NDI (%)	Survival without NDI (%)
Doyle et al. (2011) Australia	PB	500–999 g	1979–1980	348	24 months	26	100	12	6	4	NA	20	28	18 (of LB)
			1985–1987	560		38	100	14	9	1		17	18	31 (of LB)
			1991–1992	423		57	98	22	5	2		18	19	43 (of LB)
			1997	226		75	99	18	4	3		22 (BSID-II)	26	55 (of LB)
			2005	257		67	96	12	0	4		15 (BSID-III in 2005)	18	54 (of LB)
Anderson et al. (2010) Australia	PB	<28 GW and/or <1000 g	2005	221 (S at 2 years)	24 months	NA	95	9	0	2	96.9 ± 13.8 (BSID-III)	3 (BSID-III reference) 13 (controls' mean)	NA	NA
Serenius Et al. (2013) Sweden	PB	<27 GW	2004–2007	707	30.5 months	69	94	7	0.9	0.9	94 ± 12.3 (BSID-III)	6 (<72; BSID-III)	27	47 (of LB)
Toome et al.(2013) Estonia	PB	22–25 GW	2007	36	24 months	47	100	18	0	0	88.5 ± 16.7 (BSID-III)	12 (BSID-III)	24	36 (of LB)

Data are shown for CP, blindness, deafness, mean cognitive index, cognitive index <70 (<-2 SD), and NDI in survivors with a follow-up assessment.

Abbreviations: ACC indicates audit commission criteria; D, hospital discharge; FU, follow-up; LB, live births; MC, multicentre; NA, not available; OMD, Oxford minimum dataset criteria; PB, population-based; S, survivors; SC, single centre.

Inclusion criteria, definitions: Wood et al.: in children unable to complete the psychological test because of severe delay, the paediatrician estimated the child's developmental level as severely or moderately impaired; NDI defined as one that was likely to put the child in need of physical assistance to perform daily activities; Rijken et al.: NDI defined as definitely abnormal neurologic examination, MDI <-2 SD, or PDI <-2 SD; Vohr et al.: NDI defined as the presence of any of the following: moderate to severe CP, cognitive scale score <-2 SD, psychomotor scale score <-2 SD, blind in both eyes, or hearing loss requiring amplification in both ears; De Groote et al.: children unable to complete the psychological assessment test because of severe delay excluded; NDI defined as one or more severe impairments [CP (no head control, unable to

sit, dress and feed self, and walk), non-febrile seizures despite treatment, MDI and/or PDI below 55 by BSID-II, no useful hearing and/or vision]; Wilson-Costello et al.: children with congenital anomalies excluded; neurologically impaired children who were not testable with the BSID because of either behavioural problems or severe impairment, were included among those with neurologic impairment but do not have BSID scores reported; NDI defined as any major neurologic impairment, unilateral or bilateral blindness or deafness requiring a hearing aid, and/or an MDI of <70 on the BSID; Rattihalli et al.: NDI defined according to Audit commission criteria in1991–1993 and to Oxford minimum dataset criteria in 2001–2003; Doyle et al.: children with congenital anomalies excluded; children unable to complete the psychological testing because of severe delay were assigned scores of -4 SD; NDI defined as CP interfering with independent ambulation, deafness, blindness, or developmental delay below -2 SD compared with the mean for the controls; Anderson et al.: children unable to complete the psychological testing because of severe delay were assigned scores of -4 SD; Serenius et al.: children with malformations not excluded; severe disability was defined as any of the following: BSID-lll composite cognitive, language or motor score < mean-3SD, severe CP, or bilateral blindness or deafness. Moderate disability was defined as scores between −2 and −3 standard deviations from the mean of any of the BSID-III scales, moderate CP, and moderate visual or hearing impairment. Toome et al.: children unable to complete the psychological assessment test because of severe delay were assigned scores of -4 SD; NDI defined as CP interfering with independent ambulation, cognitive or language scale score of <-2 SD, hearing loss corrected with aids or deafness, blind in at least one eye).

7.2.4. Developmental outcomes

The descriptive statistics for the BSID-III composite and subtest scores for VLGA infants and FT controls are listed in Table 16. VLGA infants had significantly lower mean Cognitive, Language, and Motor Composite Scores when compared with FT control group, with the magnitude of all differences between groups in excess of approximately 0.5 SD. The estimated difference between the study groups was 8.6 points (95% CI: 5.3–11.7) for the Cognitive, 7.1 (4.0–10.2) for the Language, and 8.9 (5.3–12.5) for the Motor Composite Score. After adjustment for family income, family structure, and parents' education, the mean differences did not change. If infants with CP, blindness, and deafness were excluded, the mean group differences decreased to 5.5 (95% CI: 2.7–8.3), 4.8 (1.9–7.7), and 4.7 points (1.6–7.9), respectively.

The means (SD) of the Cognitive and Motor Composite Scores by BSID-III were significantly higher for VLGA infants born at the tertiary level maternity hospitals when compared with those born at local hospitals (95.5 (15.4) vs. 85.4 (13.4) ($p = 0.026$) and 95.5 (18.0) vs. 79.8 (17.0) ($p = 0.002$), respectively) whereas the mean Language Composite Scores were similar. P-values for the differences of the means of Cognitive and Motor Composite Scores from a multiple model adjusted for variables not under control of the clinician (GA, gender, BW $<10^{th}$ percentile, and multiple birth) remained statistically significant ($p = 0.046$ and $p = 0.010$, respectively). After adjustment, the estimated difference between the study groups was 9.2 points (95% CI: 0.2–18.2) for the Cognitive, 5.2 (-3.6–13.9) for the Language, and 13.9 (3.3–24.4) for the Motor Composite Score.

There were no significant differences in the mean composite scores between the subgroups born at 22–25 and 26–31 GW (Table 16). This may be explained by the small number of infants in the group of more immature infants, and by withdrawal of treatment in four cases during the neonatal period in the subgroup of 22–25 GW versus two cases in the subgroup of 26–31 GW.

The proportion of VLGA infants with cognitive delay was 17% (12% mild, 3% moderate, and 2% severe delay) and the proportion of VLGA infants with language delay was 33% (23% mild, 6% moderate, and 4% severe delay). Infants born at 28 to 31 GW comprised 60% of all VLGA infants with cognitive delay and 75% of all VLGA infants with language delay. Mild neurodevelopmental disability was found in 28% and NDI in 12% (5% moderate and 7% severe disability) of VLGA infants.

Previously within-group analyses for VPT children have shown a linear correlation between IQ and GA (Bhutta et al. 2002, Serenius et al. 2013). Data from the present study on the BSID-III composite scores of VLGA infants by GW are presented in Table 17 and in Figure 8. Surprisingly no linear relation between mean/median composite scores and GA was found that could be caused by the small number of infants studied.

Table 15. Differences in growth between VLGA and FT infants born in Estonia in 2007 at 2 years of CA

	VLGA infants			VLGA infants	FT infants	
	22–25 GW (n = 17)	**26–31 GW** (n = 138)	**p value**	**22–31 GW** (n = 155)	**37–41 GW** (n = 153)	**p value**
Bodyweight, g, mean (SD)	11,887 (2.056)	12,289 (1.993)	0.369	12,245 (1.997)	13,218 (1.621)	**<0.001**
Body length, cm, mean (SD)	85.6 (4.1)	86.5 (4.4)	0.344	86.4 (4.3)	87.7 (3.5)	**0.015**
Head circumference, cm, mean (SD)	47.3 (2.3)	48.8 (1.9)	**0.010**	48.6 (2.0)	49.1 (1.3)	**0.025**

Table 16. Differences in composite scores according to the BSID-III between VLGA and FT infants born in Estonia in 2007 at 2 years of CA

	VLGA infants			VLGA infants	FT infants	
	22–25 GW (n = 17)	**26–31 GW** (n = 138)	**p value**	**22–31 GW** (n = 155)	**37–41 GW** (n = 153)	**p value**
Cognitive Composite Score, mean (SD)	88.5 (16.7)	95.5 (15.1)	0.080	94.7 (15.4)	103.3 (12.9)	**<0.001**
Language Composite Score, mean (SD)	86.1 (16.9)	89.0 (14.6)	0.557	88.6 (14.9)	95.7 (12.8)	**<0.001**
Receptive Communication Score, mean (SD)	7.9 (2.6)	8.5 (2.5)	0.415	8.4 (2.5)	9.6 (2.4)	**<0.001**
Expressive Communication Score, mean (SD)	7.1 (2.9)	7.5 (2.6)	0.610	7.4 (2.6)	8.6 (2.3)	**<0.001**
Motor Composite Score, mean (SD)	86.8 (19.2)	95.3 (18.0)	0.063	94.4 (18.3)	103.3 (13.6)	**<0.001**
Fine Motor Score, mean (SD)	8.8 (3.4)	10.1 (3.2)	0.096	10.0 (3.2)	11.4 (2.7)	**<0.001**
Gross Motor Score, mean (SD)	6.6 (2.9)	8.1 (3.0)	0.065	7.9 (3.0)	9.4 (2.5)	**<0.001**

Table 17. Composite scores according to the BSID-III in VLGA infants by GA born in Estonia in 2007 at 2 years of CA

	GW								
	22–23 (n = 2)	**24** (n = 6)	**25** (n = 9)	**26** (n = 10)	**27** (n = 12)	**28** (n = 17)	**29** (n = 25)	**30** (n = 33)	**31** (n = 41)
Cognitive Composite Score, mean (SD)	80.0 (21.2)	90.8 (25.6)	88.9 (8.2)	96.0 (19.8)	88.8 (21.8)	94.4 (12.2)	98.6 (15.6)	95.2 (15.8)	96.2 (11.6)
Language Composite Score, mean (SD)	79.5 (16.3)	91.7 (26.7)	83.8 (7.3)	86.8 (17.8)	82.6 (18.6)	88.5 (13.3)	92.7 (14.7)	89.9 (17.2)	88.4 (10.2)
Motor Composite Score, mean (SD)	71.5 (23.3)	89.8 (26.9)	88.1 (12.1)	89.7 (19.1)	89.8 (23.5)	92.5 (21.7)	97.6 (15.9)	96.4 (18.3)	97.2 (15.6)

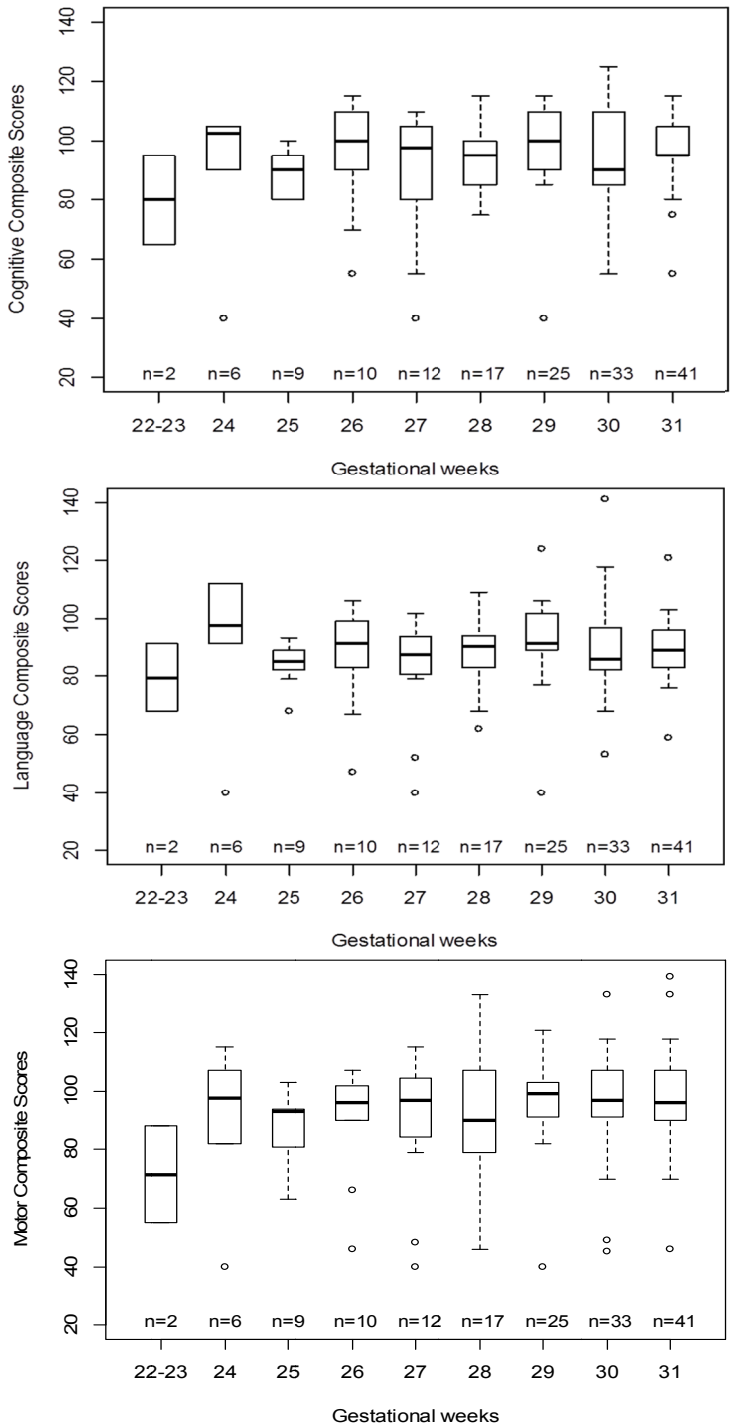
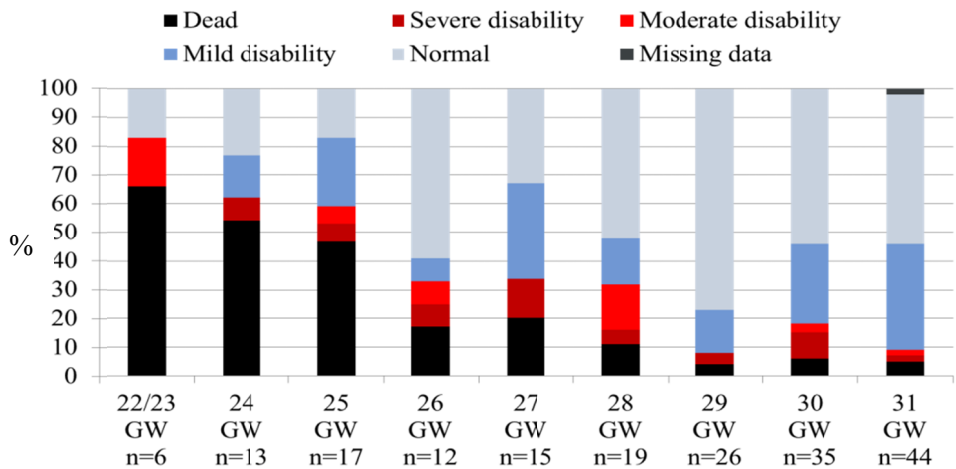


Figure 8. Median composite scores by the BSID-III for VLGA infants born in Estonia in 2007 at 2 years of CA

Consistent with previous studies (Anderson et al. 2010, Charkaluk et al. 2010), we found the Language Composite Scores to be the lowest in VLGA infants. Surprisingly, however, Language Composite Scores were also the lowest in the FT control group (Table 16). Expressive communication was delayed more than receptive communication in both groups. We speculate that the reasons for delayed development of language might include cultural differences between the populations of Estonia and the United States, given that the BSID-III was standardised in the United States and not in Estonia.

7.2.5. Composite outcome

Data on composite outcome of VLGA infants by GA are presented in Figure 9.



Definitions: the severity of the impairments are defined as follows: 1) normal development (no impairment detected in motor, cognitive, speech, hearing and ophthalmological assessment); 2) mild neurodevelopmental disability (CP with GMFCS level 1, Cognitive and/or Language Composite Scores 1 to 2 SD below norm, near normal vision and hearing); 3) moderate neurodevelopmental disability (CP with GMFCS level 2, Cognitive and/or Language Composite Scores 2 to 3 SD below norm, hearing loss corrected with aids, vision moderately reduced but better than severe visual impairment, or blind in one eye with good vision in the contralateral eye); and 4) severe neurodevelopmental disability (CP with GMFCS level 3, 4 or 5, Cognitive and/or Language Composite Score <3 SD below norm, no useful hearing even with aids, blind or can only perceive light or light-reflecting objects).

Figure 9. Survival and neurodevelopmental outcome for VLGA infants by GA born in Estonia in 2007 at 2 years of CA

Composite outcome data for VLGA infants calculated according to the different outcome measures are shown in Table 18. The proportion of infants with moderate or severe cognitive and motor delay was similar despite the outcome measurement used. However, with the use of the PSOM, language delay could be overestimated as the PSOM measures Language Deficit Production and Language Deficit Comprehensive scores separately. Additionally with the use of the PSOM, a larger proportion of infants were diagnosed with mild motor delay. Consequently, our results demonstrate that the PSOM as a stroke-specific outcome measure should be used with caution for evaluation of VPT children in general.

Table 18. Composite outcome for 155 VLGA infants born in Estonia in 2007 at 2 years of CA according to the BSID-III and the PSOM

	BSID-III reference	BSID-III control distribution	PSOM
Cognitive delay			
Mild	19 (12)	45 (29)	13 (8)
Moderate	5 (3)	7 (5)	7 (5)
Severe	3 (2)	7 (5)	8 (5)
Language delay			
Mild	36 (23)	23 (15)	39 (25)
Moderate	9 (6)	9 (6)	31 (20)
Severe	6 (4)	6 (4)	21 (14)
Motor delay			
Mild	17 (11)	23 (15)	37 (24)
Moderate	4 (3)	6 (4)	8 (5)
Severe	9 (6)	11 (7)	11 (7)

Data are shown in numbers (percentages) of examined infants.

7.2.6. Risk factors for adverse long-term outcomes

Factors that had a significant effect on the 2-year adverse outcomes (weight $<10^{th}$ percentile, CP, cognitive delay, language delay, and NDI) in the present study included antenatal steroid use, male gender, and neonatal complications such as poor neonatal growth, severely abnormal cerebral findings on neonatal ultrasound screening, BPD, and NEC (Table 19), all similar to the findings from previous studies (Ehrenkranz et al. 2006, Bode et al. 2009, Munck et al. 2010). In the present study, poor postnatal growth was associated with weight $<10^{th}$ percentile at 2 years of CA but not with a less favourable cognitive outcome, which is not consistent with the earlier literature (Ehrenkranz et al. 2006). The biggest concern is that, in spite of the withdrawal of treatment because of severe PIVH in five neonates (3% of the live-born infants), the existence of severe cerebral lesions was still the most significant risk factor for impairment among all the domains studied at follow-up. More advanced GA correlated with better composite neurodevelopment but not with each individual outcome studied.

Table 19. Prognostic factors for adverse outcomes of VLGA infants born in Estonia in 2007 at 2 years of CA

	Weight <10th percentile	**CP**	**Cognitive Composite Score <–2SD***	**Language Composite Score <–2SD***	**NDI**
			Adjusted OR (95% CI)		
GA (per week)	NS	NS	NS	NS	**0.7 (0.6–0.9)**
Antenatal steroids	**0.3 (0.1–0.8)**	NS	NS	NS	NS
Male gender	NS	NS	NS	**4.9 (1.1–21.8)**	NS
Severe cerebral lesions	**3.3 (1.0–11.2)**	**43.2 (8.2–226.5)**	**9.8 (1.9–49.5)**	**19.0 (4.8–75.1)**	**33.4 (8.6–129.9)**
BPD	**3.6 (1.5–8.7)**	NS	NS	NS	NS
NEC grade 2–3	NS	NS	**7.4 (1.5–37.2)**	NS	NS
Weight <10th percentile at discharge	**2.5 (1.1–5.4)**	NS	NS	NS	NS

*Developmental delay was calculated according to the original norms of the BSID-III.

Abbreviations: NS indicates not significant.

Definitions: BPD defined as oxygen dependency at 36 weeks' PMA; NDI defined as CP with GMFCS level 2–5, Cognitive Composite Score <–2 SD, Language Composite Score <–2 SD, hearing loss corrected with aids or no useful hearing even with aids, and/or vision moderately reduced or blind in one eye with good vision in the contralateral eye or blind or can only perceive light or light-reflecting objects; severe cerebral lesions defined as PIVH grade 3–4 and/or PVL grade 2–4, determined by neonatal cranial ultrasound scans.

Infants in the VLGA population were more likely to be from low-income families than infants in the FT population, and the parents of VLGA infants were less likely to have undertaken higher education than those of infants in the FT control group (Table 12). Although parental education level and social class have already been shown to be risk factors for poor cognitive development of premature children at the age of 2 years (Fily et al. 2006, Charkaluk et al. 2010), in our study population the demographic variables did not affect the results. On average, the children in the present study stayed at home with their mothers for an extended period of time after their birth (Table 12). Staying at home without exposure to a more diverse and stimulating environment should increase the effect of parental education level on a child's development. Nonetheless, in the present study, the latter effect might have been diminished by the impact of perinatal risk factors or might become significant during later stages of development.

7.3. Acute respiratory morbidity during the first two years of life in very low gestational age infants in Estonia

7.3.1. Frequency of respiratory infections

The mean annual number of RI was 1.5 during the first and 1.9 during the second year of life in the VLGA as well as in the 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 (Table 20). The frequency of annual RI divided into none, 1–3, and >3 episodes was similar between the VLGA and the FT group during the first as well as the second year of life. The proportion of infants with RI during the first year of life was higher among those initially discharged between April and September as compared with those discharged from October to March (72 vs. 59%; $p = 0.008$).

In the present study, we describe lower mean annual number of RI for VLGA infants as well as for FT infants than in the United States (5.1 episodes per child-year during the first three years of life) and 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) (Chonmaitree et al. 2008, Gruber et al. 2008). 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 (Marbury et al. 1997, Gruber et al. 2008). In the present 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 contrast, in the Netherlands, 66% of 12 months old children attended day care (van Putte-Katier et al. 2012). Another factor in the low rate of RI that should

be noted is retrospective design of parental interviews, which may potentially miss some mild cases of RI and thus lead to the under-reporting of RI.

7.3.2. Wheezing

Compared with FT, VLGA infants had, due to RI, more wheezing episodes including RW. Furthermore, those born at 22–27 GW had more RW than those born at 28–31 GW (Table 20). 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%; 3.31; 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%; 1.51; 0.87–2.62 and 10 vs. 5%; 2.40; 0.93–6.21, respectively).

Depending on the country, study design, and year, at least one episode of wheezing has been described in 15–39% (Latzin et al. 2007, Garcia-Marcos et al. 2010) of children during the first years of life with the occurrence of RW in 12–36% of children (Garcia-Marcos et al. 2010). In addition, wheezing and RW are more common in premature infants as compared with FT infants, occurring in up to 40–68% and 13–25%, respectively (Greenough et al. 2005, Holditch-Davis et al. 2008, Pramana et al. 2011). Similarly, a higher prevalence of wheezing 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 (Greenough et al. 2005, Latzin et al. 2007, Holditch-Davis et al. 2008, Garcia-Marcos et al. 2010, Pramana et al. 2011). It can be suggested 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 (Rosenthal et al. 2010), wheezing and prematurity have been associated with respiratory morbidity in future life (Metsala et al. 2008). Whether a relatively low frequency of RI and wheezing episodes in our study cohort might predict better long-term respiratory health, needs further long term studies.

7.3.3. Hospitalisation and antibiotic consumption

During the study period there were altogether 149 hospital admissions in the VLGA and 69 in the FT group. The overall hospitalisation rate and that due to RI was significantly greater in VLGA than FT infants (Table 21). 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 a higher frequency of bronchitis or bronchiolitis in VLGA infants

(Table 21). No differences between those born at 22–27 GW and 28–31 GW were observed. Among VLGA infants, the 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 the hospitalisation rate was also greater in VLGA infants without BPD compared to FT infants (28 vs. 18%; 1.79; 1.02–3.17). Only one infant in the VLGA group was admitted to the paediatric intensive care unit due to RI.

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 countrywide 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 GW, 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 (Lamarche-Vadel et al. 2004). Similarly, in a study from the United States (Smith et al. 2004) 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 VPT 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 (Latzin et al. 2007, Pramana et al. 2011).

The odds of receiving antibiotics due to RI were 2.1 times greater for VLGA as compared with FT infants (Table 21). 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%; 1.53; 0.95–2.46).

Routine antibiotic use for viral RIs is not recommended in evidence-based clinical practice guidelines (Wong et al. 2006). Nevertheless, despite the rarity of serious bacterial infections, antibiotics are frequently used in children younger than 24 months (Adcock et al. 1998). 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.

Table 20. RI in VLGA and FT infants born in Estonia in 2007 during the first two years of life

	VLGA infants			VLGA infants	FT infants	
	22–27 GW (n = 39)	**28–31 GW** (n = 116)	**OR or IRR* (95% CI)**	**22–31 GW** (n = 155)	**37–41 GW** (n = 153)	**OR or IRR* (95% CI)**
Cumulative number of all acute illnesses						
during the first two years of life per 100 infants	408	340	1.20 (0.91–1.59)*	357	353	1.01 (0.85–1.21)*
1st year of life	210	141	**1.49 (1.04–2.14)***	159	155	1.02 (0.80–1.30)*
2nd year of life	197	198	1.00 (0.71–1.39)*	198	198	1.00 (0.82–1.22)*
Cumulative number of RI						
during the first two years of life per 100 infants	382	321	1.19 (0.90–1.58)*	336	336	1.01 (0.83–1.21)*
1st year of life	200	134	**1.50 (1.02–2.19)***	150	148	1.01 (0.79–1.30)*
2nd year of life	182	187	0.97 (0.69–1.36)*	186	188	0.99 (0.80–1.22)*
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)*
1st 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)*
2nd 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)
1st year of life	13 (33)	41 (35)	0.91 (0.42–1.97)	60 (39)	55 (36)	1.13 (0.71–1.79)
2nd 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)**
RW, n (%) of infants	10 (26)	11 (9)	**3.29 (1.27–8.51)**	21 (14)	7 (5)	**3.27 (1.35–7.14)**

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

Table 21. Hospitalisations and antibiotic consumption in VLGA and FT infants born in Estonia in 2007 during the first two years of life

	VLGA infants			VLGA infants	FT infants	
	22–27 GW (n = 39)	**28–31 GW** (n = 116)	**OR (95% CI)**	**22–31 GW** (n = 155)	**37–41 GW** (n = 153)	**OR (95% CI)**
Hospitalisations						
Cumulative number of all hospitalisations during the first two years of life per 100 infants	133	84	**1.59 (1.01–2.52)**	96	45	**2.13 (1.48–3.06)**
Cumulative number of hospitalisations due to RI during the first two years of life per 100 infants	62	47	1.30 (0.70–2.41)	51	25	**2.00 (1.19–3.35)**
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						
Upper respiratory tract infections, n (% of hospitalisations)	4 (17)	18 (33)		22 (28)	18 (46)	
Bronchitis/bronchiolitis, n (% of hospitalisations)	16 (67)	25 (45)	p = 0.176*	41 (52)	11 (28)	**p = 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						
Cumulative number of courses of antibiotics during the first two years of life per 100 infants	200	137	1.46 (0.98–2.17)*	153	125	1.22 (0.91–1.63)*
1st year of life	90	56	1.60 (0.95–2.70)*	65	47	1.37 (0.92–2.04)*
2nd year of life	110	81	1.36 (0.88–2.10)*	88	78	1.13 (0.83–1.53)*
Cumulative number of courses of antibiotics due to RI during the first two years of life per 100 infants	182	129	1.41 (0.93–2.12)*	143	122	1.22 (0.87–1.59)*
1st year of life	77	49	1.57 (0.90–2.73)*	56	44	1.37 (0.83–1.93)*
2nd year of life	105	80	1.31 (0.86–2.00)*	86	77	1.12 (0.82–1.53)*
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)**
1st 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)
2nd 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)**

*The distributions of the reasons for hospitalisations were compared by Fisher exact test.

7.3.4. Risk factors for recurrent respiratory infections and adverse outcomes of respiratory infections

The associations between the risk factors and unfavourable outcomes of RI as derived from the multiple logistic regression models are shown in Table 22. No associations were found between any of the investigated risk factors and the occurrence of recurrent RI. In the multiple analyses of the whole study population including both VLGA and FT infants, 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. In multiple 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 (4.96; 1.46–16.83). Male gender, prematurity, and BPD were independent risk factors for hospitalisation in the whole study cohort and again, in the VLGA group, GA (as a continuous variable) and male gender were not associated with hospitalisations due to RI, whereas BPD appeared to be a significant risk factor (3.20; 1.40–7.33).

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 (Latzin et al. 2007, de Martino and Ballotti 2007, Gruber et al. 2008, Holditch-Davis et al. 2008, Garcia-Marcos et al. 2010, de Pramana et al. 2011, van Putte-Katier et al. 2012). 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 (de Martino and Ballotti 2007, Garcia-Marcos et al. 2010). Surprisingly, in the present study only four risk factors – low maternal education, male gender, prematurity, and the presence of BPD – were found to be significant for unfavourable outcomes of RI whereas BPD was the only risk factor for all of them.

Table 22. The associations between prognostic factors and unfavourable outcomes of RI during the first two years of life in the whole study cohort of VLGA and FT infants born in Estonia in 2007

	At least 1 wheezing episode		**RW (≥3 episodes)**		**Hospitalisation**	
	OR (95% CI) (Simple analysis)	**OR (95% CI)** (Multiple analysis)	**OR (95% CI)** (Simple analysis)	**OR (95% CI)** (Multiple analysis)	**OR (95% CI)** (Simple analysis)	**OR (95% CI)** (Multiple 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)**
BPD	**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)**

Abbreviations: NS indicates not significant.

Definitions: BPD defined as oxygen dependency at 36 weeks' PMA; higher education defined as higher professional education or university degree.

8. GENERAL DISCUSSION

8.1. The outcome of very preterm infants as an indicator of quality of care in Estonia

Study II is the first nationwide study from an Eastern European country that reflects the recent changes in patient characteristics, management, morbidity, and outcome until death or discharge home for VLGA infants. The results of the study show an improvement in perinatal management of VLGA infants: a higher proportion of infants were born by caesarean section and received antenatal corticosteroids, maternal antibiotics, and/or surfactant therapy, whereas a lower proportion of infants had an Apgar score <5 at 1 minute. The most important finding is the improved survival of VLGA infants, whereas morbidity at discharge and the length of hospital stay remained unchanged. Furthermore, the improved survival was achieved in conjunction with less invasive neonatal treatment: a lower proportion of VLGA infants was intubated after birth, treated with antibiotics or inotropes, or mechanically ventilated, and ventilation was of shorter duration. It is noteworthy that these improvements of care were achieved with relatively limited resources. In 2006, healthcare expenditure in Estonia in terms of purchasing power parity per capita, had increased to US$ 996 but still remained three times lower than the figure for states that were members of the European Union before 2004 (World Health Organization Regional Office for Europe 2007).

Survival

Over the study periods, the rate of survival until discharge increased significantly, up to 85% among all VPT live births in Estonia. This may be attributable to a principle of antenatal regionalisation, proactive perinatal management, active admittance of infants for care, and an established national consensus on aims of treatment, as well as to improvements in technology and expertise. The 51% survival rate achieved for infants born at 22–25 GW in the later cohort 2007–2008 is good when compared with similar published population-based studies, which have reported rates between 31% and 40% (Table 7), although Nordic countries report higher rates (Markestad et al. 2005, Fellman et al. 2009). The study demonstrates that achieved survival rates in Estonia are comparable to those obtained in developed countries (Tables 6 and 7).

Regionalisation and onsite neonatal units

Healthcare and health-system factors play a role in the outcome of VLGA infants more generally; for example, Marlow et al. (Marlow et al. 2014) have now published data on the outcome of all 2,460 EPT births in England from the cohort born in 2006. The study showed that, first, with antenatal transfer of mother to a tertiary centre there were fewer intrapartum or labour ward deaths. Second, where infants remained behind in lower level services, overall mortality proved to be higher than for those infants in tertiary level services. And finally, tertiary level services with the highest activity had fewer deaths

than tertiary services with a lower workload of EPT infants. Also, a much-quoted German study (Poets et al. 2004) concentrated on babies born in units with a NICU versus those born in units without a NICU and showed better outcomes in the former category. Poets and his colleagues (Poets et al. 2004) recommended that, to achieve best outcomes, neonatal units should look after at least 36 to 50 VLBW infants annually. Additionally, the separation of VPT infants from their mothers directly after birth could bring along many unfavourable consequences (Flacking 2012).

Therefore, one of the indicators of the quality of care of VPT infants is the proportion of VPT births delivered in maternity units with an onsite NICU. The organisation of care for these infants varies greatly in Europe (Van Reempts et al. 2007). According to the data from the EURO-PERISTAT Project in 2010, there was a wide variation in the proportion of VPT babies born in the highest level of care. This percentage ranged from about 20 to 100%, whereas only 22.5% of all VPT infants were born at the highest level of care in Estonia (EURO-PERISTAT Project 2010). The principal difficulty in interpreting this indicator is the absence of consensus definition of an "onsite NICU" and levels of neonatal care. For instance, in the EURO-PERISTAT Project these data were collected and presented on local classifications of units. Only 16 from 29 participating countries in the project were able to provide some data about this indicator (EURO-PERISTAT Project 2010). While it is easy to agree on what constitutes a tertiary or regional centre with full neonatal intensive care facilities, many countries, including Estonia, have intermediate levels of care that provide care to many, but not all, high-risk infants.

In the present study, 90% of VPT infants were born in 2007–2008 at tertiary level maternity hospitals, which allowed them to receive optimal obstetrical care. However, higher rates of antenatal transfers have been reported in Norway (Markestad et al. 2005) and Portugal (Neto 2006). A high degree of centralisation of VPT births in Estonia may result in lower effectiveness because of the necessity for postnatal transport of VPT newborns. Almost half of the VLGA infants in Studies I and II were transferred postnatally to the regional children's hospitals during the first hour of life and only a quarter of infants were cared for at least first 48 hours of life in the NICUs of the tertiary level maternity hospitals. The absence of onsite neonatal units which provide full intensive care, including MV, and the disunity of the higher level neonatal care can be considered to be a weakness in the delivery of perinatal care in Estonia.

Nonetheless, drawing practical conclusions from the published data about the effectiveness of perinatal regionalisation (Lasswell et al. 2010), namely to rigorously centralise perinatal care, meets resistance abroad (Poets 2014) as well as in Estonia. A mixture of hurt professional bride and a struggle for market share, that means economic rather than quality-related reasons could be the most obvious reasons for this resistance (Poets 2014). In Finland, for example, a country with an area nine times and with a population five times than of Estonia, provision of the highest level neonatal care is concentrated to only five centres, with many patients having long distances to cover (Lehtonen

et al. 2011). In contrast, in Estonia with a much lower annual number of VPT births, VPT infants are cared for in seven units with different levels of neonatal intensive care. Another good example beside Finland is Portugal, probably the European country that has made the largest step forward in reducing infant mortality and reorganising perinatal care (Neto 2006).

Proactive perinatal management

A study from Sweden showed that a proactive perinatal strategy increases the number of live births and improves the postnatal condition and survival of EPT infants without an increase in morbidity (Hakansson et al. 2004). In Estonia, a significant improvement in the administration of antenatal steroids, antibiotics, and delivery by caesarean section was noticed for births at 26–31 GW but not at <26 GW. It could be speculated that more proactive obstetrical management could improve the outcome, at least for infants born at 24–25 GW. An active approach by paediatricians resulted in a higher frequency of admittance for care and in a trend towards better survival of infants born before 26 GW in 2007–2008 as compared with 2002–2003.

Neonatal morbidity

VPT infants with major neonatal morbidities have an increased risk of adverse long-term outcome. Brain injury, BPD, severe ROP, neonatal sepsis, and NEC have been shown to be predictive of poor long-term outcome (Schmidt et al. 2003, Bassler et al. 2009). Thus, all of these conditions were included in the analysis of morbidity-free survival in the present study. Overall, 42% of VLGA infants who were born in 2002–2003 and 44% of those born in 2007–2008 in Estonia survived until discharge without major early morbidities.

The short-term morbidity rates for VPT infants in the current study were higher than in other reports, especially the rate of severe PIVH, ROP, and NEC (Darlow et al. 2003, Vanhaesebrouck et al. 2004, Markestad et al. 2005, Tommiska et al. 2007, Fischer et al. 2009, EXPRESS 2010, Murphy et al. 2010, Zeitlin et al. 2010a) (Tables 6 and 7). Part of this difference can be explained by antenatal characteristics, because the incidence of prolonged PPROM was higher and the use of maternal antibiotics and antenatal corticosteroids lower in our cohorts than in those reported by others (EXPRESS 2010, Murphy et al. 2010, Stoll et al. 2010). The high incidence of PIVH, which was found to be the main risk factor for death as well as for all studied unfavourable neuro-developmental outcomes, can be related partly to transport during the early postnatal period (Palmer et al. 2005, Mohamed et al. 2010). The significant decrease in PIVH grade 3–4 among the survivors of birth at 22–25 GW between 2002–2003 and 2007–2008 can be explained by the trend to withdraw treatment from VLGA infants with confirmed PIVH grade 4. The most striking difference compared to the reports from high income countries, which was seen in the incidence of ROP, might in part be explained by the absence of national guidelines for oxygen therapy during the study period, as changes in oxygen supplementation can decrease the incidence of ROP (Sears et al. 2009).

The most immature infants accounted for most of the difference in morbidity with the previously reported studies (Table 7), which suggests a need for continued attention to the quality of care and reinforcement of evidence-based guidelines for this group.

Two-year outcome

In Study III, the national cohort of VLGA infants showed impairments in cognitive and language development, as well as in fine and gross motor functions, when compared with the FT control group, whereas 11% of VLGA infants had CP and 12% had NDI. Growth failure was also a significant problem among VLGA infants. Among all domains studied, the main risk factor for an adverse outcome was the existence of severe neonatal cerebral lesions.

The higher prevalence of CP found in the present study (90.9 per 1,000 live births) than in Western Europe in 1995 (58.0 per 1,000 live births) (Platt et al. 2007) can only partly be explained by a lower level of experience in Estonia as compared with Western Europe in taking care of infants at the borderline of viability, because 65% of infants with CP were born at 28 to 31 GW. The other possible explanations for the higher rate of CP in our population are the short study period, different perinatal characteristics, and the need for postnatal transport of infants in Estonia. The latter has been shown to be associated with an increased risk of PIVH (Mohamed and Aly 2010), which in turn was the main risk factor for CP and other adverse outcomes in the present study.

Direct comparisons with various studies of the cognitive impairment of VLGA infants are difficult to perform because the inclusion criteria, assessment tests, and definitions used differ among studies. When reporting developmental outcomes, it is critical to include the whole population as the mean scores will be affected by the exclusion of children who function below the lower limit of the test. For example, with the age banding used in the 30 month assessment as part of the EPICURE study of 283 children of 25 GW or less (Wood et al. 2000), 33 children (11.7%) had scores lower than 50. Without this group, the mean (SD) BSID-II MDI of these was 84 (12) or 1 SD below the standardisation mean. Nominally assigning a score of 40 to the excluded children brought this down to 77. Additionally it should be noted that in the present study, for the FT control infants, the means of the scaled composite scores and subtest scores by the BSID-III were comparable to (Bode et al. 2009) or lower (Anderson et al. 2010, Moore et al. 2012, Serenius et al. 2013) than those reported previously.

Nonetheless, it can be cautiously concluded, that when compared with previously reported studies (Tables 13 and 14), the VLGA population of the present study, which was outborn and included infants with congenital malformations as well as infants who functioned below the lower limit of the BSID-III, had a comparable or worse (Bode et al. 2009, Anderson et al. 2010, Munck et al. 2010, Moore et al. 2012, Voigt et al. 2012, Serenius et al. 2013) but still satisfactory outcome, despite the recent argument that the BSID-III underestimates developmental delay (Anderson et al. 2010, Moore et al. 2012). The

proportion of infants with NDI was in accordance with recent studies (Bode et al. 2009, Munck et al. 2010). As a whole, the 2-year cognitive outcome results reflect a satisfactory level of quality of care for VPT infants in Estonia.

Availability, effectiveness, and efficiency of neonatal care in Estonia

Availability of neonatal intensive care for VLGA infants in the present studies can be determined, firstly, by the proportions of infants offered intensive care, and secondly, by the proportion of infants born at the third level maternity hospitals. The proportions of newborns offered intensive care increased significantly over time from 2002–2003 to 2007–2008 in Estonia. The decision to offer intensive care to ELGA/VLGA live births largely reflects paediatric decision-making, although obstetric management sometimes takes precedence, particularly if a decision has been reached not to offer intensive care already before birth. Not all ELGA infants will benefit from intensive care; those with lethal malformations and those of extreme immaturity are some examples. None of these infants were excluded from the present studies. Hence, 100% of ELGA infants will never be offered intensive care. However, in the Estonian cohort of VLGA infants born in 2007–2008, 98% of infants were admitted to the neonatal intensive care, so there is no opportunity for the rate of offered intensive care to increase. On the contrary, for infants born before 24 GW, the survival until discharge was less than 50% and the adverse outcome at the CA of 2 years was 80%. The intensive treatment for babies born at 22–23 GW might not be appropriate in Estonia and health professionals should discuss with the parents the provision of only palliative care for these most immature infants.

The proportion of VLGA infants born outside tertiary level maternity hospitals was relatively low in Estonia, 13 % in 2002–2003 and 10% 2007–2008. However, infants born at local hospitals had significantly lower scores on BSID-III cognitive and motor composite scores at 2 years of CA compared to infants born at tertiary maternity hospitals. These disadvantages emphasise the need for VLGA infants to be born at tertiary level maternity hospitals in Estonia. Nevertheless, as it has been discussed in the section of "Regionalisation and onsite neonatal units", regionalisation in Estonia may result in lower effectiveness because of the necessity for postnatal transport. We could not analyse the impact of early postnatal transfers in our study cohorts as none of the infants requiring the highest level of care with MV were cared for in the tertiary level maternity hospitals. Nevertheless, we suggest that one way to improve morbidity-free survival rates in Estonia is to establish perinatal centres with onsite neonatal units with full intensive care, including MV and neonatal surgery.

In the framework of the present studies, the effectiveness of perinatal and neonatal care can be evaluated only through the changes in the short-term outcome over the two studied periods 2002–2003 and 2007–2008 as the long-term outcome was not studied over time. In Estonia, the survival rate for VLGA infants until discharge, which is a measure of the effectiveness of neonatal intensive care within a geographical region, increased significantly. The gain in survival was similar for infants born before 26 GW and for those born at 26–

31 GW. Morbidity-free survival and the incidence of major neonatal morbidities, predicting poor neurodevelopmental outcome, was not significantly different between the two studied cohorts, except for a decrease in PIVH grade 3–4 in the cohort born in 2007–2008. On the other hand, it is noteworthy that survival until discharge increased without concomitant increases in neonatal morbidity and the length of hospital stay. Nevertheless, since the rates of neonatal morbidities and neurosensory impairment at 2 years of CA were clearly too high, and as mortality rates have fallen, the greatest challenge for neonatal services in Estonia is to improve the outcomes of neonatal intensive care by reducing the prevalence of major early morbidities for VLGA infants.

Efficiency of neonatal intensive care has not been studied in Estonia and should be a key priority to research in the future.

8.2. Current position of routine data collection of outcome for very preterm infants in Estonia

The present studies highlight the importance of establishing nationwide datasets in Estonia for collection of perinatal and neonatal data until hospital discharge and follow-up data at 2 years of CA for VLGA infants.

After the pilot-period in 2007–2008, the national neonatal research register called "Vastsündinu tervise andmekogu" was not permitted to continue by the Estonian Data Inspectorate. Furthermore, the neonatal research register was held by the enthusiasm of physicians and no national financial support was found to continue with the dataset. Estonian Medical Birth Registry has collected data about all births in Estonia since 1992. However, the register is designed to measure fertility and it collects principal data until the end of the early neonatal period. Still in 2014, there are no national datasets specifically designed for collection of neonatal data until hospital discharge and follow-up data for VLGA infants in Estonia; none of the units is participating in the international neonatal networks. However, Estonia is participating with a 12-month national cohort of VLGA births from 2011–2012 in the project of Effective Perinatal Intensive Care in Europe to explore the outcome of VLGA infants and the use of evidence based practices for the care of VLGA infants during the recent years (EPICE project 2014).

Monitoring of variations in mortality and morbidity rates for VLGA infants is important as they indicate changes in practice that may improve outcome. In addition, the information on late morbidity in survivors of neonatal intensive care is needed for several target groups: 1) parents, to understand the possible consequences of survival of their baby and accept informed decisions about their child's care; 2) the clinical team, for sharing with parents, evaluating their service, and research; 3) commissioners of neonatal care and other services for children so that they can make informed decisions and plans; and 4) general public so they can take part in an informed debate on priorities in healthcare (Rattihalli et al. 2011).

8.3. Impact of the studies on follow-up of very preterm infants in clinical practice in Estonia

Neurologic sequelae and developmental disorders are among the complications with the greatest influence on long-term quality of life. Screening for these developmental anomalies must therefore be a major objective in the follow-up of VPT infants, and care after discharge is now considered a critical part of the neonatal intensive care service. However, these follow-up programmes are costly, time-consuming, and might cause unnecessary anxiety to parents and children. Therefore, there is a need to identify precisely which children have to be included in such programmes.

In the Study III, more advanced GA correlated with better composite neurodevelopment but not with each individual outcome studied. EPT infants comprised only a minority of infants with growth failure, CP, or other problems as cognitive and language developmental delay. In addition, even infants who were free of neurosensory impairment had significantly worse scores in cognitive, language, and motor development than FT control infants. As a consequence, in response to the understandable concern about EPT infants, the results support the recommendation to monitor all VLGA infants in clinical practice, at least in Estonia.

Despite the absence of national follow-up register for VPT infants in Estonia, these infants are followed in everyday clinical practice until the CA of 2 years according to national follow-up guidelines (Toome et al. 2008). Since 2009, the BSID-III has been used in the routine clinical follow-up programme of high-risk, including VLGA, infants to assess their cognitive, language, and motor development.

In the Study IV, a similar frequency of RI among VLGA and FT infants during the first two years of life was observed. 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 and/or diagnosed with BPD. 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 multiple 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.

Consequently, from a clinical point of view the results of Study IV suggest a tailored approach when planning hospital discharge of VLGA infants. Special attention should be targeted to the parents of infants with BPD or born before 28 GW in counselling to limit the exposure of their children to respiratory viruses and environmental risk factors. Additionally, the resources in preventing respiratory viruses should be allocated, first of all, to VLGA infants with BPD and to those born before 28 GW.

8.4. Suggestions for future improvement in the quality of care for very preterm infants in Estonia

The challenge for perinatal services in Estonia is to decrease long-term disability in VPT infants without compromising their survival. Given that the rate of VPT live births in Estonia is within the range of other European countries, and that improvement of the socio-environmental milieu requires time, there is an urgent need for a reduction in neonatal morbidity in order to improve the long-term outlook for VLGA infants.

Focusing on the improvement of outcome, we propose the following approaches to increase morbidity-free survival of VLGA infants in Estonia.

First is the ongoing implementation of the evidence-based national guidelines to unify the policies of different units. Following completion of the present studies, hospitals in Estonia have already implemented guidelines for neonatal resuscitation, oxygen therapy with saturation targets, introduction of early CPAP in the delivery room, etc. Nevertheless, these guidelines have to be unified on the national level. In 2014, the Estonian Ministry of Social Affairs and the Estonian Perinatal Society called together a team of specialists to establish national guidelines with respect to the management of the VPT delivery and birth in the country.

Second, the official levels of perinatal and neonatal care (Riigi Teataja 2004) in Estonia should be re-evaluated and maximally two perinatal centres should be established that offer all the services of third level antenatal and perinatal care and have onsite neonatal units to provide full intensive care. This will reduce the need for postnatal transfers and will improve the collaboration of antenatal staff with neonatologists with regard to the timing of birth and appropriate perinatal care. Introducing a better regionalisation of perinatal care requires binding rules and regulations. This is a task for regulatory bodies, for example, the government, not for obstetricians or neonatologists (Poets 2014).

Third approach is to establish the ongoing surveillance of outcomes and iatrogenic factors that might have detrimental effects on the health of VPT infants. For example to incorporate an additional data file with important variables on all VPT infants to the Estonian Medical Birth Registry and to collect the data until the infant's PMA of 44 weeks' gestation. Furthermore, it is unarguable that each unit that delivers VPT babies must audit short-term and long-term outcomes and be ready to produce them for benchmarking. The general public require to be informed about the mortality and morbidity figures for the units within their region. Audit must be robust and universal. All centres should be benchmarking their data on the national level as well as with some system which has been extensively validated, for example, the Vermont Oxford Network (Laing 2014).

8.5. Strengths and limitations of the studies

Since the introduction of antenatal steroids and postnatal surfactant therapy in perinatal treatment of VPT infants, studies from developed countries have presented population-based outcomes for EPT and VPT infants (Tommiska et al. 2001, Darlow et al. 2003, Larroque et al. 2004, Vanhaesebrouck et al. 2004, Markestad et al. 2005, Tommiska et al. 2007, Fischer et al. 2009, EXPRESS GROUP 2010, Murphy et al. 2010, Zeitlin et al. 2010, Rüegger et al. 2012). However, although some data are available (Gadzinowski et al. 2010), no nationwide studies have been published from Eastern European countries, which have more limited resources and less experience in the care of EPT infants than high income countries. The latter ascribe the importance to the present studies, which to our knowledge, are the first nationwide short-term and long-term outcome studies of VLGA infants from an Eastern European country. Our epidemiological data and the insight into perinatal services in Estonia will be useful for other middle income countries for comparison.

The main strength of our studies is the nationwide population-based design that gives a complete picture of the outcome for all VPT births during the study periods and thus ensures the provision of detailed information, first, for use in prenatal counselling and decision-making by physicians and families, and second, for benchmarking the quality of care of VPT births in Estonia. Additionally, the use of GA as an inclusion criterion enabled a large group of VPT infants to be studied and reduced the proportion of infants who were small for their GA. The other strengths of the studies are the use of standardised methods for follow-up, the inclusion of an age, gender, and geographic location matched control group of FT infants in Studies III and IV, and the attainment of follow-up rates that were close to 100%. The high follow-up rate eliminates potential bias in the interpretation of the outcomes caused by the possible neurodevelopmental morbidity among infants lost to follow-up.

We acknowledge some limitations of the study, which include:1) the retrospective nature of the data that relate to the earlier cohort of VLGA infants born in 2002–2003 in Study II; 2) a relatively small study cohort in subgroups of EPT infants particularly in Studies III and IV; 3) the short-term outcome for VLGA infants was analysed from live-born infants whereas to benchmark perinatal services more precisely, there is a need to evaluate all stillbirths where the foetus is alive at the onset of the delivery; 4) the BSID-III had not been standardised previously for use in Estonia; 5) CP was chosen as an index of long-term outcome, which could lead to an underestimation of motor disability; 6) the retrospective design of parental interviews in Study IV and not collecting data about relevant childhood immunisations and common environmental risk factors for RI, like paternal smoking and presence of pets at home; and 7) the low statistical power using multiple risk-adjustment methods based on a single year to detect predictors for unfavourable outcomes. However, we believe that the abovementioned limitations did not preclude us from drawing adequate conclusions.

8.6. Suggestions for future research

The present studies raise several questions for future research:

- Neonatal intensive care for VLGA infants in Estonia should be re-evaluated at intervals in the future to ensure that its effectiveness and availability are maintained. Beside survival rates, morbidity and length of hospital stay until discharge and neurosensory impairment and developmental disability rates at the CA of 2 years, the quality-adjusted survival rate, another measure of the increasing effectiveness of neonatal intensive care within a geographical region, should be evaluated over time.
- One tool that is being used to improve complex medical care processes is comparing the performances of different hospitals and learning from the better performing centres. Therefore, centre-differences in care and outcome should also be evaluated in Estonia.
- The efficiency of perinatal and neonatal care as well as of follow-up programmes for VPT infants has never been evaluated in Estonia. Since there have been large increases in effectiveness during the last decade, one suggestion for future research is to determine the efficiency as well as the changes in efficiency of neonatal intensive care for VPT infants in Estonia.
- In the present study, the outcome for VLGA infants was evaluated until the CA of 2 years. However, the predictive validity of developmental testing at 2 years of age for cognitive, behavioural, and learning problems might be poor (Hack et al. 2005b). Whilst the authors of early studies sought to catalogue the severe neurological and sensory disabilities associated with VPT birth, recent research has highlighted a range of more subtle deficits and has shown that the nature of impairment may be changing (Aylward 2003). Cognitive and behavioural problems are among the most common adverse outcomes and such "higher prevalence/lower severity" impairments are more evident at school age, even in those who are free of neurosensory impairments. To provide a more complete picture of longer-term effects on the survivors, follow-up studies for children born VPT through the school years are needed in Estonia.
- The studied cohorts of VLGA infants born in 2002–2003 and 2007–2008 are the first ones with systematically collected perinatal and neonatal data in Estonia. The latter offers an opportunity to study different aspects of associations of prognostic factors and health outcomes beside neurosensory and developmental impairment.

9. CONCLUSIONS

1. The nationwide studies of short-term outcome for VLGA infants showed that:
   1.1. The rate of VLGA births in Estonia during the studied periods (11.3 per 1,000 live births in 2002–2003 vs. 10.2 in 2007–2008) has remained unchanged, whereas the outcome for VLGA infants has improved since 2002.
   1.2. With proactive perinatal management, active admission of VLGA infants to intensive care, and less invasive neonatal care, survival for VLGA live births until discharge increased significantly from 78% in 2002–2003 up to 85% in 2007–2008 without concomitant increases in neonatal morbidity and the length of hospital stay.
   1.3. During the later study period 2007–2008, there were centre differences in the early neonatal management of VLGA infants.

2. The nationwide follow-up studies for VLGA infants at the CA of 2 years showed that:
   2.1. No impairment was found in 60% of the VLGA infants. NDI was noted in 12% of VLGA infants, with 8% of the infants affected by CP without independent walking, 5% with cognitive delay, 10% with language delay, and 1% with hearing impairment.
   2.2. In all domains studied regarding neurodevelopment and growth, adverse conditions were more prevalent among VLGA infants than among the FT control group. The differences between VLGA and FT infants in terms of the mean Cognitive, Language, and Motor Composite Scores assessed using the BSID-III scales were in excess of 0.5 SD. Among all the VLGA infants, 31% were below the 10^{th} percentile of expected bodyweight.
   2.3. The frequency of RI during the first two years of life, in general, was similar among VLGA and FT infants, except for those born at 22 to 27 GW. Nevertheless, VLGA infants, especially these born before 28 GW and/or diagnosed with BPD, had more wheezing episodes and hospitalisations due to RI than their FT counterparts.

3. In the present studies, seven prognostic factors for death until hospital discharge and for the presence of growth failure and an adverse neurodevelopmental outcome at the CA of 2 years as well as for unfavourable outcomes of RI were found:
   3.1. GA and male gender were the only significant neonatal characteristics for adverse outcome (GA for death, bodyweight $<10^{th}$ percentile, and NDI, and male gender for language development delay).
   3.2. From perinatal characteristics, low Apgar score at birth was a risk factor for death and antenatal corticosteroids were protective against growth failure.

3.3. The most significant risk factor of different adverse outcomes found was the presence of major neonatal morbidities. Severe PIVH and/or PVL were associated with death, bodyweight <10th percentile, and all studied adverse neurodevelopmental outcomes, whereas BPD was associated with bodyweight <10th percentile and all unfavourable outcomes of RI. NEC was a significant risk factor for cognitive development delay.

4. From a clinical point of view the results of the studies suggest two main recommendations:
   4.1. Not only ELGA, but all VLGA infants should be monitored in a clinical practice at least the first two years of life. The recommendation is based on the following: 1) in the follow-up study regarding growth and neurodevelopmental outcome, GA did not correlate with each individual outcome studied among VLGA infants; 2) ELGA infants comprised only a minority of infants with growth failure, CP, and developmental problems; and 3) even infants who were free of neurosensory impairment had significantly worse scores in cognitive, language, and motor development than infants from the FT control group.
   4.2. Regarding the prevention of RI among VLGA infants, the results suggest a tailored approach when planning hospital discharge of VLGA infants. Special attention should be targeted to the parents of infants with BPD or born before 28 GW in counselling to limit the exposure of their children to respiratory viruses and environmental risk factors. Additionally, the resources in preventing respiratory viruses should be allocated, first of all, to VLGA infants with BPD and to those born before 28 GW.

5. As a whole, the results reflect a satisfactory level of quality of care for VLGA infants in Estonia. Despite the improved survival of VLGA infants, the morbidity rates of infants were similar or higher when compared with comparable data from high-income countries. Consequently, the greatest challenge for perinatal and neonatal services in Estonia is to improve the long-term outcome for VLGA infants by reducing the prevalence of major early morbidities. The main requirements for that in Estonia are the ongoing implementation of evidence-based practices, reorganisation of perinatal care by establishing two perinatal centres that offer tertiary level neonatal intensive care on site, and ongoing surveillance of iatrogenic factors that might have detrimental effects on the health of VLGA infants.

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11. SUMMARY IN ESTONIAN

Väga väikese gestatsioonivanusega enneaegsed lapsed Eestis: ravitulem ja prognostilised tegurid

Maailmas sünnib ligikaudu 11% lastest enneaegsena, enne 37 gestatsiooninädala (GN) täitumist (Blencowe *et al.* 2012). Seejuures toimub enne 32 GN täitumist e väga väikesel gestatsioonivanusel (VVGV) vaid 1–1,5% kõigist sündidest, kuid see lastegrupp on eriti õrn ja moodustab umbes pooled vastsündinu- ja imikuea surmajuhtudest (EURO-PERISTAT Project 2010). Perinataalabi ja vastsündinute intensiivravi areng on märkimisväärselt suurendanud VVGV vastsündinute elulemust, kuid kaasa toonud ka laste kroonilised terviseprobleemid, suured ravikulud, perede häiritud psühhosotsiaalse toimetuleku ning lapse edasise elu jooksul kumuleeruvad ühiskonna kulutused.

Tänapäevase meditsiiniabi põhiprintsiibiks on pakkuda kvaliteetset ravi. Peri- ja neonataalabi tundlikuks kvaliteediindikaatoriks on VVGV laste ravitulem. Üldtunnustatult peegeldab peri- ja neonataalabi kvaliteeti VVGV enneaegsete laste tervis 2-aastaselt korrigeerituna enneaegsusele sünnil. Selleks vanuseks on enamus puuetest diagnoositavad ning lapse areng ei ole mõjutatud niivõrd sotsiaalsetest teguritest – nt vanemate haridusest ja sotsiaalmajanduslikust toimetulekust – kui peri- ja neonataalperioodi ravi kvaliteedist (Lyon 2007). Uuringutega on tõestatud erinevate neonataalsete haiguste (bronhopulmonaalne düsplaasia, (peri)intraventrikulaarne ajuhemorraagia, periventrikulaarne leukomalaatsia, nekrotiseeriv enterokoliit, sepsis ja enneaegsuse retinopaatia) põdemisel esinev risk VVGV laste hilisematele puuetele ja arenguhäiretele (Schmidt *et al.* 2003, Bassler *et al.* 2009).

1980.–1990. aastate murrangulised avastused olid aluseks enneaegsete vastsündinute tänasele intensiivravile, eelkõige antenataalne glükokortikoidravi laste suremuse vähendamisel ning haigestumise ennetamisel ja postnataalne surfaktantravi hingamishäirete ravis. 21. sajandil on tõenduspõhine VVGV vastsündinu vähe-invasiivne sünnijärgne ravitaktika, eriti kopsude mehaanilise ventilatsiooni vajaduse ennetamine (Sweet *et al.* 2013). Ravikvaliteedi kõrval mõjutab laste tervisetulemit oluliselt perinataalabi ja vastsündinute intensiivravi korraldus. Väga enneaegsete sünnituste koondamine III etapi ravivõimalustega ja piisava enneaegsete vastsündinute arvuga keskustesse vähendab laste suremust ja haigestumist, kusjuures mõjutavateks teguriteks peetakse nii III etapi keskuste kogemust kui vastsündinu sünnijärgse varase transpordi potentsiaalset negatiivset toimet (Rautava *et al.* 2007, Lasswell *et al.* 2010, Mohamed *et al.* 2010).

1992. aastal võeti Eestis kasutusele Maailma Terviseorganisatsiooni enneaegsuse kriteerium (22–36 GN) ning alustati < 1000 g sünnikaaluga ja enne 28 GN täitumist sündinud laste sünni registreerimist ja ravi. Kiire tehnilise arengu ning teadmiste ja kogemuste täiustumise tulemusel on < 1000 g sünnikaaluga vastsündinute varane neonataalsuremuskordaja aastatel 1992–2012 vähenenud Eesti meditsiinilise sünniregistri andmetel ligi 9 korda. 1990-ndatest

aastatest toimib Eestis enne 34. GN toimuvate sünnituste tsentraliseerimine III etapi sünnitusmajadesse ning kasutusel on tänapäevased tõenduspõhised ravivõtted. Eestis puuduvad aga perinataalsed keskused, mistõttu III astme intensiivravile ja/või pikemale haiglaravile kuuluvad vastsündinud tuleb transportida III etapi sünnitusmajadest kahe lastehaigla lasteintensiivravi või vastsündinute osakonda.

Uurimistöö eesmärgid

Perinataalabi ja vastsündinute intensiivravi kvaliteedi ning korralduse hindamisel peetakse üliolulisteks rahvastikupõhist peri- ja neonataalabi näitajate seiret. Eestis puudusid edasivaatavalt kogutud rahvastikupõhised andmed VVGV vastsündinute ravitulemi kohta, mistõttu uurimistöö üldeesmärgiks oli kirjeldada VVGV laste ravi varast ja hilist tulemit Eestis.

Töö alaeesmärgid olid:

1. Kirjeldada aastatel 2007–2008 sündinud VVGV vastsündinute varast ravitulemit (intensiivravile suunamine, suremus, neonataalne haigestumine, ravitoimingud, haiglaravi kestus ja keskustevahelised erinevused) esmase haiglaravi lõpul (uuring I) ja leida muutused VVGV sündide osakaalus ning laste varases ravitulemis võrreldes aastatel 2002–2003 sündinud laste võrdluskohordi tulemiga (uuring II).
2. Kirjeldada 2007. aastal sündinud VVGV laste ravi hilistulemit enneaegsusele korrigeeritud 2 aasta vanuses ning võrrelda andmeid ajalisena sündinud ja individuaalselt sobitatud võrdluskohordi laste tulemiga (uuring III).
3. Kirjeldada VVGV laste ägedat respiratoorset haigestumist kahel esimesel eluaastal ning võrrelda ajalisena sündinud laste haigestumisega (uuring IV).
4. Leida riskitegurid VVGV laste surmaks ja ebasoodsaks tervisetulemiks enneaegsusele korrigeeritud 2 aasta vanuses (uuring II, III).
5. Leida riskitegurid kahe esimese eluaasta ägeda respiratoorse haigestumise ebasoodsaks kuluks (uuring IV).
6. Hinnata tervikuna peri- ja neonataalabi kvaliteeti Eestis ning leida teed ravikvaliteedi edasiseks parandamiseks.

Patsiendid ja metoodika

Käesolev uurimus oli rahvastikupõhine edasivaatav kohortuuring, mis hõlmas aastatel 2007–2008 elusalt sündinud VVGV laste kohorti ning koosnes neljast alauuringust.

Uuring I ja II

Varase ravitulemi hindamiseks analüüsiti 2007.–2008. aastal elusalt sündinud 360 VVGV lapse kohorti ning muutuste leidmiseks ajas võrreldi 2002.–2003. aastal elusalt sündinud 264 VVGV lapse kohordiga. Lapsi jälgiti esmase haigla-

ravi lõpuni, välja arvatud enneaegsuse retinopaatia diagnoosimisel, mil lapsi jälgiti võrkkesta täieliku vaskulariseerumiseni. 2007.–2008. aasta kohordi andmed saadi uuringuregistrist „Vastsündinute tervise andmekogu", kuhu raviarstid sisestasid edasivaatavalt laste ravijuhtude andmed. Küsimustik koosnes 68 tunnusest raseduse ja sünnituse kulu, sünni, lapse sünnijärgse transpordi, peamiste neonataalsete haiguste, ravitoimingute ja tulemi kohta. Andmekogu töötas internetipõhiselt, töös järgiti isikuandmete kaitse nõudeid ja andmekogu oli registreeritud Andmekaitse Inspektsioonis. Kogutavate tunnuste definitsioonid olid eelnevalt määratletud. Varasema kohordi laste andmed sisestati uuringuregistrisse tagasivaatavalt.

Uuring III ja IV

2007. aastal elusalt sündinud 187 VVGV last moodustasid alakohordi, kelle ravi hilistulemit (uuring III) ja ägedat respiratoorset haigestumist kahel esimesel eluaastal (uuring IV) hinnati laste enneaegsusele korrigeeritud 2 aasta vanuses. Antud vanuses elus olnud 156-st lapsest osales uuringus 155 (99%), sest üks pere oli Eestist lahkunud.

Laste tervisetulemit ja ägedat respiratoorset haigestumist võrreldi ajalisena (≥ 37 GN) sündinud laste võrdluskohordi tulemustega. Igale VVGV lapsele sobitati sünnitushaiglate andmebaaside alusel kaks ajalisena sündinud last vastavalt järgnevatele kriteeriumidele: 1) ajalised lapsed olid sündinud esimestena peale VVGV lapse oodatavat sünnikuupäeva samas geograafilises piirkonnas; 2) nad ei vajanud esimesel elunädalal ravi; ja 3) olid sobitatud VVGV lapse soo ja rahvusega. Kui kahest individuaalselt sobitatud ajalisest lapsest esimese vanemad keeldusid uuringus osalemast, siis pöörduti teise lapse vanemate poole. Kahel juhul ei soovinud uuringus osaleda kumbki pere. Seega kokku osales hilistulemi uuringutes 153 ajalisena sündinud last. Uuringust III ja IV ei arvatud välja oluliste kaasasündinud väärarenditega VVGV lapsi ning ajalisena sündinud lapsi, kellel oli diagnoositud arengut potentsiaalselt mõjutav haigus peale esimest elunädalat.

Laste enneaegsusele korrigeeritud 2 aasta vanuses (± 1 kuu) kutsuti uuritavad järelkontrolli ühte kahest uuringukeskusest, Tallinna Lastehaiglasse või Tartu Ülikooli Kliinikumi lastekliinikusse. Hinnati laste somaatilist, neurosensoorset ja arengulist tulemit. Laste kaalu, pikkust ja peaümbermõõtu mõõdeti tavapäraste mõõtmisvahenditega. Laste arengut hindas psühholoog standardiseeritud Bayley testi 3. versiooni abil (Bayley 2006), mille alusel saadi koondskoorid kognitiivsele, kõne ja motoorsele arengule ning alatesti skoorid retseptiivsele ja ekspressiivsele kõnele ning peen- ja jämemotoorikale. Neuroloogilist leidu hindas lasteneuroloog. Tserebraalparalüüs defineeriti vastavalt Euroopa tserebraalparalüüsi seire töögrupi klassifikatsioonile (Surveillance of Cerebral Palsy in Europe 2000) ning motoorse funktsiooni hindamisel kasutati jämemotoorika hindamise skaalat (*Gross Motor Function Classification System,* GMFCS*;* Palisano et al. 1997). Paralleelselt kirjeldatud meetoditega kasutati ka pediaatrilise insuldi tulemi mõõdikut (*Paediatric Stroke Outcome Measure,*

PSOM; de Veber *et al.* 2000). Andmed nägemis- ja kuulmispuude kohta saadi laste kliinilisel järelkontrollil teostatud uuringutest.

Kognitiivse, kõne ja motoorse arengu mõõdukas/raske mahajäämus diagnoositi juhul, kui vastavad koondskoorid olid < -2 SD hinnatuna Bayley testi järgi. Mõõdukas/raske arenguhäire defineeriti juhul, kui lapsel esines vähemalt üks järgnevatest kriteeriumidest: tserebraalparalüüs (GMFCS-skaala 2.–5. aste), kognitiivse arengu mõõdukas/raske mahajäämus, kõne arengu mõõdukas/raske mahajäämus, raske nägemispuue ja/või raske kuulmispuue.

Ravi ebasoodsaks hilistulemiks laste enneaegsusele korrigeeritud 2 aasta vanuses loeti kaalu < 10 protsentiili vastavalt eesti 0–2 aastaste laste kasvukõveratele ja/või tserebraalparalüüsi, kognitiivse arengu mõõduka/raske mahajäämuse, kõne arengu mõõduka/raske mahajäämuse ja/või mõõduka/raske arenguhäire esinemist.

Äge respiratoorne haigestumus selgitati vanemate küsitluse teel tagasivaatavalt järelkontrolli päeval, hospitaliseerimised täpsustati haiglate andmebaasidest. Ägeda respiratoorse haigestumise ebasoodsaks kuluks loeti kas ühekordse või korduva vilistava hingamise esinemist ja/või haiglaravi vajadust.

Andmeanalüüs tehti programmiga Stata 12 (StataCorp LP, College Station, Texas).

Uuringud kiitis heaks Tartu Ülikooli inimuuringute eetika komitee ning uuringus III ja IV osalenud laste vanema(te)lt võeti informeeritud nõusolek.

Peamised tulemused

VVGV enneaegsete laste varane ravitulem esmase haiglaravi lõpul

Eestis sündis elusalt 360 VVGV last aastatel 2007–2008 ja 264 last aastatel 2002–2003, moodustades 1,1 ja 1,0% kõikidest elussündidest (p = 0,184). Hilisemas perioodis oli suurem mitmikute osakaal ja emade keskmine vanus. Samuti oli VVGV sündide perinataalne käsitlus proaktiivsem hilisemal perioodil: antenataalselt rakendati enam loote kopsude ettevalmistamist glükokortikoidiga (73 *vs* 81%; p = 0,020) ja antibakteriaalset ravi (37 *vs* 55%; p < 0,001) ning oluliselt rohkem VVGV lapsi sündis keisrilõike teel (42 *vs* 54%; p = 0,005). Perinataalne käsitlus oli proaktiivsem eeskätt küpsemate, 26.–31. GN sündinud laste seas. Kaasuvalt vähenes antud gestatsioonivanuste vahemikus sündinud laste osakaal, kelle Apgari hinne oli 1. eluminutil väiksem kui 5.

Mõlemal uuringuperioodil sündis Eestis ligikaudu 90% VVGV lastest III etapi naistekliinikus, kuid ligikaudu pooled neist vajasid esimesel elutunnil kohest transporti lastehaiglasse ning vaid neljandik lastest transporditi lastehaiglasse peale 48. elutundi.

Võrreldes varasema perioodiga 2002–2003 suunati aastatel 2007–2008 enam VVGV lapsi intensiivravile (94 vs 98%; p = 0,013) ning oluliselt suurenes ka elulejate osakaal kõigist VVGV elussündidest (78% *vs* 85%; p = 0,041). Elulemuse paranemisega ei kaasnenud hilisemaid puudeid ennustavate neonataalsete haiguste esinemise suurenemist. Aastatel 2002–2003 ja 2007–2008

oli ≥ II staadiumi nekrotiseerivat enterokoliiti ja positiivse verekülviga hilist sepsist põdenud VVGV laste osakaal vastavalt 7 *vs* 12% (p = 0,055) ja 23 *vs* 22% (p = 0,692) elusalt sündinud VVGV lastest. Ellujäänud VVGV lastest põdesid antud ajaperioodidel bronhopulmonaalset düsplaasiat hapnikravi vajadusega 36. postmenstruaalnädalal 20 *vs* 24% (p = 0,388), III–IV astme (peri)intraventrikulaarset hemorraagiat 9 *vs* 5% (p = 0,058), II–IV astme periventrikulaarset leukomalaatsiat 7 *vs* 4% (p = 0,068) ja ≥ III staadiumi enneaegsuse retinopaatiat laserravi vajadusega 11 *vs* 11% (p = 0,886) lastest.

Elulemuse suurenemine saavutati vähem invasiivse neonataalse raviga: hilisemas perioodis oli väiksem laste osakaal, kes vajasid esimesel elutunnil endotrahheaalset intubatsiooni ning kogu esmase haiglaravi jooksul inotroopset ravi, kopsude mehaanilist ventilatsiooni ja/või antibakteriaalset ravi. Samuti lühenes kopsude mehaanilise ventilatsiooni ja antibakteriaalse ravi kestus. VVGV laste varases sünnijärgses ravitaktikas ilmnesid aastatel 2007–2008 olulised keskustevahelised erinevused. Nimelt kasutati ühes kolmest III astme naistekliinikus sünnijärgsete hingamishäirete ravis oluliselt enam pideva positiivse rõhu varast rakendamist, millega kaasus kopsude ventilatsiooni vajaduse oluline vähenemine esmase haiglaravi jooksul.

Aktiivsema perinataalabi käsitluse, VVGV laste elulemuse suurenemise ja vähem invasiivse neonataalravi rakendamisega ei kaasnenud aastatel 2007–2008 haiglaravi kestuse suurenemist võrreldes aastatega 2002–2003.

Mitmesel regressioonanalüüsil olid peamised riskitegurid surmaks väike gestatsioonivanus sünnil (OR 0.66; 95% CI 0.57–0.75), 1. eluminuti Apgari hinne < 5 (2.67; 1.49–4.79) ja III–IV astme (peri)intraventrikulaarse hemorraagia esinemine (8.79; 4.71–16.42).

VVGV enneaegsete laste ravi hilistulem enneaegsusele korrigeeritud 2 aasta vanuses

Uuringus III ja IV osalenud VVGV kohordis oli mitmikute osakaal suurem kui ajalisena sündinud laste võrdluskohordis. Samuti olid VVGV lapsed enam pärit madala haridustaseme ja sissetulekuga peredest. VVGV laste keskmine vanus rinnapiimaga toitmise lõpetamisel oli oluliselt väiksem (147 *vs* 308 päeva; p < 0,001) ja lastekollektiivi minekul oluliselt suurem (22,2 *vs* 20,4 kuud; p < 0,001) kui ajalisena sündinud lastel.

Järelkontrollil olid 60% VVGV lastest arengus järele jõudnud ajalisena sündinud eakaaslastele ning neil ei esinenud nägemis- ja kuulmispuuet. Mõõdukas/raske arenguhäire esines 12%-l VVGV lastest: tserebraalparalüüs 8%-l, kognitiivse arengu mõõdukas/raske mahajäämus 5%-l, kõne arengu mõõdukas/raske mahajäämus 10%-l ja kuulmispuue 1%-l. Vaid üks laps oli pime ühest silmast. Väike kaal (< 10 protsentiili) esines kolmandikul ja lühike pikkus ning väike peaümbermõõt ligikaudu viiendikul VVGV lastest.

VVGV laste tervisetulem oli halvem kõikides uuritud valdkondades võrreldes ajalisena sündinud lastega. Enneaegsete laste kõik kolm kasvumõõtu (kehakaal, pikkus ja peaümbermõõt) olid statistiliselt tõepäraselt väiksemad kui aja-

liselt sündinud lastel. Bayley testi alusel hinnatud kognitiivse, kõne ja motoorse arengu keskmine koondskoor oli VVGV lastel 0,5 SD võrra madalam kui ajalisena sündinud lastel. Enneaegsetel lastel oli eriti täheldatav kõne arengu hilinemine. Keskmiste koondskooride vahe VVGV ja ajalistel lastel püsis muutumatuna kohandamisel pere sissetulekule, pere struktuurile ja vanemate haridusele ning vähenes, kuid jäi statistiliselt tõepäraseks, kui analüüsist arvati välja tserebraalparalüüsi ning raske nägemis- ja kuulmispuudega lapsed. III etapi naistekliinikutes sündinud VVGV laste kognitiivse ja motoorse arengu keskmised koondskoorid olid oluliselt kõrgemad kui maakonnahaiglates sündinud VVGV lastel.

Mitmesel regressioonanalüüsil leiti peamised riskitegurid ebasoodsaks tulemiks enneaegsusele korrigeeritud 2 aasta vanuses (kaal < 10 protsentiili, GMFCS-skaala 2.–5. astmega tserebraalparalüüs, kognitiivne areng < -2 SD, kõne areng < -2 SD ja/või mõõdukas/raske arenguhäire). Nendeks osutusid antenataalse glükokortikoidravi puudumine, neonataalsel aju ultraheliskriiningul diagnoositud III–IV astme (peri)intraventrikulaarne ajuhemorraagia ja/või II–IV astme periventrikulaarne leukomalaatsia, bronhopulmonaalse düsplaasia ja/või nekrotiseeriva enterokoliidi põdemine esmasel haiglaravil ning ebarahuldav kaaluiive sünnijärgses perioodis. Gestatsioonivanus pideva tunnusena oli oluliseks riskiteguriks koondtulemile mõõduka/raske arenguhäirena, kuid mitte väikese kaalu, tserebraalparalüüsi, kognitiivse arengu mahajäämuse ja kõne arengu mahajäämuse esinemisele laste 2 aasta vanuses.

VVGV enneaegsete laste äge respiratoorne haigestumus kahel esimesel eluaastal

Haigestumus ägedatesse respiratoorsetesse infektsioonidesse ei erinenud VVGV ja ajaliste laste seas. Esimesel eluaastal esines mõlemas grupis keskmiselt 1,5 ja teisel eluaastal 1,9 ägeda respiratoorse infektsiooni juhtu. Küll aga esines esimesel eluaastal ägedat respiratoorset haigestumist oluliselt enam < 28 GN sündinud lastel kui küpsematel enneaegsetel ja ajalistel lastel. Ägeda respiratoorse haigestumise ajal esines VVGV lastel oluliselt enam vilistavat hingamist ning nad vajasid ka enam antibakteriaalset ja haiglaravi.

Mitmesel regressioonanalüüsil oli ägeda respiratoorse haigestumise ebasoodsa kulu (ühekordne vilistav hingamine, korduv vilistav hingamine ja/või hospitalisatsiooni vajadus) olulisteks riskiteguriteks ema madal haridustase, meessugu, enneaegsus ja bronhopulmonaalse düsplaasia põdemine esmasel haiglaravil, kusjuures ainsaks oluliseks riskiteguriks kõikidele ägeda respiratoorse haigestumise ebasoodsa kulu tunnustele oli bronhopulmonaalse düsplaasia esinemine.

Järeldused

1. Uuritavatel ajaperioodidel, 2002–2003 *vs* 2007–2008, püsis VVGV elussündide osakaal Eestis muutumatuna, kuid oluliselt suurenes VVGV vastsündinute intensiivravile suunamine (94 *vs* 98%) ja laste elulemus esmase

haiglaravi lõpuni (78 *vs* 85%). VVGV laste elulemuse suurenemine saavutati aktiivsema perinataalraviga ja vähem agressiivse vastsündinute raviga. Aastatel 2007–2008 esinesid keskustevahelised erinevused sünnijärgsete hingamishäirete varases ravitaktikas. Elulemuse paranemisega ei kaasnenud hilisemaid puudeid ennustavate haigustega elulejate osakaalu suurenemist ega haiglaravi kestuse pikenemist.

2. 2007. aastal sündinud ja enneaegsusele korrigeeritud 2 aasta vanuses uuritud VVGV lastest 12%-l esines mõõdukas/raske arenguhäire; 60% oli arengus järele jõudnud ajalisena sündinud lastele. Bayley testi alusel hinnatud kognitiivse, kõne ja motoorse arengu keskmine koondskoor oli VVGV lastel 0,5 SD võrra madalam kui ajalisena sündinud lastel. VVGV laste kõik kolm kasvumõõtu (kehakaal, pikkus ja peaümbermõõt) olid statistiliselt tõepäraselt väiksemad kui ajaliselt sündinud lastel. VVGV lastel esines ägeda respiratoorse haigestumise korral oluliselt enam vilistavat hingamist ning antibakteriaalse ja haiglaravi vajadust.
3. VVGV enneaegsete laste ebasoodsa hilise tervisetulemi peamiseks riskiteguriks oli hilisemaid puudeid ennustavate neonataalsete haiguste põdemine esmasel haiglaravil, kusjuures bronhopulmonaalse düsplaasia põdemine oli ainsaks oluliseks riskiteguriks laste ägeda respiratoorse haigestumise ebasoodsa kulu kõikidele tunnustele.
4. Perinataalabi ja vastsündinute intensiivravi kvaliteeti Eestis saab hinnata rahuldavaks. VVGV laste elulemus Eestis on võrdväärne teiste arenenud meditsiiniabiga riikidega, kuid laste varane haigestumus ja tervisehäirete esinemine 2 aasta vanuses jääb osaliselt suuremaks.
5. Peri- ja neonataalabi peamiseks ülesandeks Eestis on vähendada VVGV enneaegsete neonataalset haigestumist, säilitades suure elulejate osakaalu. Ravikvaliteedi edasiseks parandamiseks on vajalik ravitaktika ühtlustamine riikliku tõenduspõhise enneaegse sünnituse ja vastsündinu käsitlusjuhise väljatöötamisega ning väga enneaegsete sünnituste jätkuv koondamine III etapi raviasutustesse. Oluline on perinataalkeskuste loomine, et tagada loote ja vastsündinu tõenduspõhise ravi järjepidevus ning välistada VVGV enneaegsete transport vahetus sünnijärgses perioodis. Nüüdisaegse kiiresti muutuva perinataalabi ja vastsündinute intensiivravi tingimustes tuleb leida võimalus väga enneaegsena sündinud laste ravikvaliteedi järjepidevaks seireks Eestis.

12. ACKNOWLEDGEMENTS

This thesis is based on studies that would not have been possible without the co-operation of a large number of people throughout Estonia. Generating the database of the care for newborns called „Vastsündinu tervise andmekogu" has required an enormous amount of work by many physicians in NICUs of different levels all over the country. I feel priviledged to have had the opportunity to use this database for research purposes and I am deeply grateful to all of you. This database led me to the next steps in research.

Additionally, I would like to express my gratitude to all the parents and their newborn children with whom I have shared the moments of joy and grief in the unit in which I have worked for more than 25 years, for being the primary source of inspiration in my research. Particularly, I would like to acknowledge all of the infants and their parents who participated directly in my studies.

When working on this thesis, I have received valuable help from many people.

- I am priviledged to have had two excellent supervisors supporting and guiding me through this journey.

  I owe my deepest gratitude to my primary supervisor Docent Heili Varendi for the commitment. You have been there for me as a supervisor and as a friend. You have always found time for me, even during evenings, weekends, and holidays.

  I also owe my deepest gratitude to Anneli Kolk, MD, PhD. Thank you for the positive attitude.
- I thank the reviewers Professor Raul-Allan Kiivet and Docent Oivi Uibo for the in-depth revision of the thesis and for the constructive criticism that substantially improved the final result.
- These studies were carried out in a truly multidisciplinary team. I am grateful for the dedicated efforts of the staff within the neonatal units in Estonia for their practical help with the data collection. I especially wish to express my gratitude to the members of the national neonatal register team – Pille Andresson, Mari-Liis Ilmoja, Eha Kallas, Kati Korjus, Lea Maipuu, Pille Saik, Heili Varendi, and Mari-Anne Vals –, and to the members of the national follow-up team for VLGA infants – Birgit Kaasik, Anneli Kolk, Inna Marats, Mairi Männamaa, Svetlana Müürsepp, Marileen Olenko, Haide Põder, Triinu Tänavsuu, Tiina Valvas, Mari-Anne Vals, and Heili Varendi.
- I wish to express my sincere gratitude to the co-authors of the original publications: Pille Andresson, Mari-Liis Ilmoja, Anneli Kolk, Irja Lutsar, Mairi Männamaa, Silvi Plado, Inge Ringmets, Pille Saik, Triinu Tänavsuu, Mari-Anne Vals, and Heili Varendi. I admire the enthusiasm, commitment, and will of all of you, to work in every possible way to improve the quality of care of preterm babies, and also carry the responsibility of offering follow-up and support for those infants and their families. In particular, I thank Professor Irja Lutsar for being the expert I could always ask for help.

- I am deeply indebted to Inge Ringmets and Pille Kool for their help with statistics for the studies. You have been most patient in answering my questions and that has provided me with an opportunity to learn a lot.
- I thank Professor Vallo Tillmann, Docent Tuuli Metsvaht, and Docent Emeritus Anne Ormisson, for a thoughtful review of the manuscripts. In particular, I would like to thank Anne Ormisson, my first teacher in neonatology during the university years.
- I would also like to express my sincere gratitude to all of the dear colleagues and staff from the Unit of Newborns and Infants, Tallinn Children's Hospital, for taking care of my clinical commitments while I was away from clinical work. I am proud to be a part of this team. Thank you all: Haide, Merle, Ilona, Reelika, Priit, Svetlana, Marleen, Marina, and all the others.
- My warmest thanks go to my previous colleagues in my clinical work – Adik Levin, Eve Rattasep, Anna Potapova, and Kaja Leito. I have learned so much from your warm-hearted way of working with newborn babies and their families.
- I am grateful to „my perinatal father" Ragnar Tunell and „my perinatal mother" Professor Liisa Lehtonen. Your wisdom taught me to see the woods when I have only seen the trees.
- I gratefully acknowledge the Social Welfare and Health Care Board of Tallinn City Government and Tallinn Children's Hospital for sponsoring the national neonatal research register and Tallinn Children's Hospital Foundation for supporting the process of organising clinical follow-up for VLGA infants. Many thanks to Mall-Anne Riikjärv, MD, PhD, and Katrin Luts, MD, for having a head of a unit who has been a lot of away from the clinical work and even for supporting me under these circumstances.
- I also wish to thank all my friends for tolerating me through those busy years and for reminding me of things other than work. Particularly Karin, Kersti, Kaja, Reet, Kati, Külli, Anti, Mirjam, Anders, Annika, Kadri, Riina, and Kairit.
- I am grateful to my parents Silvia and Mihkel Veiderma, for providing a loving home in my childhood and for placing a high value on education. I have also been lucky to have „extra-parents" – Silvi, Lembit, Leida, Koidu, and Karla – and two sisters – Anne and Riin – and their families. Thank you all for your love, support, and endless patience.
- Above all, my greatest gratitude goes to my family – to my supporting and loving husband Valdo, who still, after 30 years of our marriage, is full of childish, romantic, and adventurous surprises for me, and to my sons Joosep and Jaagup. You are my life, everything else is just a job. Or is not it?

These studies were supported by the grant GARLA 7094 from the Estonian Science Foundation and by the grant No. 2695 from the Estonian Ministry of Education and Science.

PUBLICATIONS

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Education:

1967–1979	Tallinn Secondary School 21
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1985–1987	Internship in paediatrics, Tallinn Children's Hospital
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Professional employment:

1987–	Tallinn Children's Hospital, Unit of Newborns and Infants (1997–2011 Senior Paediatrician, since 2011 Head of the Unit)

Membership:

1986–	Estonian Paediatric Association
1988–	Estonian Medical Association
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Social activities:

1990–2000	Member of the Estonian Breastfeeding Promoting Committee
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2007–2010	President of Tallinn Paediatric Association
2013–	President of Estonian Paediatric Association
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Training outside Estonia:

1991	Finland, Kuopio University Hospital
1992	Norway, Bergen University Hospital
1994	Sweden, different children's hospitals
1997	USA, Pittsburg, Allegheny Hospital
2001	Sweden, different children's hospitals

Scientific work:
Main fields of research: quality improvement in neonatology, follow-up studies of preterm infants, ethical decision-making questions in neonatal intensive care, family-centered care.

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2003–	Eesti Lastearstide Seltsi Sertifitseerimiskomisjoni liige
2007–2010	Eesti Lastearstide Seltsi Tallinna osakonna juhtaja
2013–	Eesti Lastearstide Seltsi president
2013–	Euroopa Pediaatria Akadeemia rahvuslik delegaat

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1994	Rootsi, erinevad lastehaiglad
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3 rahvusvahelise eelretsenseeritava artikli, 40 rahvusvahelise või Eesti konverentsi teeside ja 12 artikli autor *Eesti Arstis*.

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