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ORIGINAL ARTICLE



Trends in neonatal morbidity and mortality for very low birthweight infants: a 20-year single-center experience

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ABSTRACT:

Objective: To describe trends in mortality and morbidity rates of very low birth weight infants as well as their pre-, peri- and postnatal characteristics over a period of 20 years' time.

Methods: Retrospective study in all very low birth weight infants admitted to the neonatal intensive care unit of the University Hospitals Ghent from 1 January 2000, to 31 December 2020. Mortality was the primary outcome variable with major morbidities being co-primary outcome variables. Pre-, peri- and postnatal characteristics are secondary outcome variables. We compared pre-, peri- and postnatal characteristics, as well as major morbidities between different groups with comparable rates of mortality.

Results: We included a total of 2037 very low birth weight infants and divided them in 3 epochs based on stepwise reductions in mortality in 2008 and 2013: 2000–2007 ($n = 718$), 2008–2012 ($n = 506$) and 2013–2020 ($n = 813$). Mortality decreased significantly over the years in all gestational ages, but predominantly in those with the youngest gestational age. Changes in obstetric and neonatal care were observed over time. Most significant changes were the increased use of antenatal corticosteroids, magnesium sulfate and surfactant. Intraventricular hemorrhage grade III/IV decreased significantly in all gestational ages. Significant increase in retinopathy of prematurity was observed. Bronchopulmonary dysplasia at 36 weeks and discharge home with oxygen is increasing in the total group. In those born below 26 weeks a slight increase in all major morbidities was observed especially of patent ductus arteriosus and retinopathy of prematurity. Increase of all other major morbidities seems to stabilize in epoch 3. The number of infants surviving without any major morbidity increases to almost 1/2 in all very low birth weight infants and to 1/10 in those born 24–25 weeks gestation.

Conclusion: Analysis of the real-life experience showed that survival in very low birth weight infants significantly increased over time. Evolution of major morbidities will have to be carefully watched in the future.

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Introduction

Prematurity is a global health problem. Even though very low birth weight (VLBW) infants (= birth weight (BW) < 1500 grams) only represent 1.2% of live births, they are the leading cause of neonatal mortality [1–2]. Considerable progress has been made in the approach of VLBW infants in the last two decades. Reported data over the past years show decreased mortality in VLBW infants, but there is also concern that this will result in more infants surviving with major short- and long-term morbidities [3–6]. The availability of these data is important for the society. The proportion of infants surviving with/without major morbidities is

also important to clinicians in guiding families with VLBW infants. Registries and networks that benchmark outcomes of VLBW infants can be helpful in evaluating trends in mortality and morbidity [7–9]. The objective of this study is to describe mortality and morbidity rates in VLBW infants as well as their pre-, peri- and postnatal characteristics over the past 20 years.

Methods

Retrospective chart review on VLBW infants admitted to the NICU of the University Hospitals Ghent, Flanders, Belgium from 1 January 2000, to 31

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December 2020. All data were extracted from the database NICaudit[®], a national database set up by the national college of “Mother and Newborn” in 2001 [10]. All perinatal items entered in the database were isolated as indicators of quality of care and strictly defined by the members of the College and invited experts from the Belgian Society of Neonatologists. Only NICU admissions were entered in the database, i.e. life born infants with active treatment. Data could be extracted in a separate file by using the search function. No infants were excluded in this analysis to represent the real-life data in our quaternary unit. Data were available up to discharge from the NICU.

Mortality was the primary outcome variable with major morbidities being co-primary outcome variables. Pre-, peri- and postnatal characteristics were secondary outcome variables. We compared pre-, peri- and postnatal characteristics, as well as major morbidities between different groups with comparable rates of mortality.

Prenatal characteristics included preterm labor, pre-eclampsia, chorioamnionitis, antenatal corticosteroids, tocolysis, multiple pregnancy, primigravida and spontaneous pregnancy. Analyzed characteristics at birth were gestational age (GA), BW, gender, cesarean section, presence of life-threatening congenital malformations, and the fact that neonates were outborn or not. Postnatal characteristics included duration of invasive mechanical ventilation and parenteral nutrition, administration of postnatal corticosteroids and surfactant, and regional transfer at discharge. Major morbidities included clinical or confirmed late-onset infection, persistent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) any stage as well as the subgroups stage I-II and stage III-IV, periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD) at 36 weeks' gestation, discharge home with oxygen, retinopathy of prematurity (ROP) $\geq$ stage 3, presence of congenital life-threatening congenital malformations and mortality. Definitions of late-onset infection are in accordance to the national surveillance of nosocomial infection in NICU's in Belgium (Neo-KISS). Clinical infection was defined as an infection where at least 5 days of antibiotics were required based on at least two of the following signs or symptoms: 1) fever, instable temperature, hypothermia; 2) tachycardia > 200 beats/minute or new or increased bradycardia < 80 beats/minute; 3) recapillarization > 2 s; 4) new or increased apneas > 20 s; 4) unexplained metabolic acidosis BE < 10 mEq/L; 5) new hyperglycemia > 140 mg/dL; 6) other signs such as skin color, increased oxygen requirement

(intubation), unstable condition or apathy. In clinical infections no pathogens were detected in blood culture, nor was there an apparent infection at another site. Confirmed infection was defined as an infection confirmed by positive blood culture. PDA was clinically suspected and echocardiographically confirmed, i.e. transductal diameter > 1.5 mm with left-right shunting. NEC was defined as NEC Bell stage I to IV. Periventricular leukomalacia was defined as persistent periventricular flaring > 7 days, ventriculomegaly > 10 mm, echo densities on brain ultrasound exam or signs of periventricular or subcortical leukomalacia on brain MRI, as well as a combination of any of these findings. BPD was defined as the need for oxygen and/or any respiratory support at 36 weeks.

Most variables were presented as binary variables (Yes/No), except for GA, BW, duration of ventilation, and duration of parenteral nutrition. For statistical analysis, Pearson Chi-Square test and one-way ANOVA were used. The cutoff for statistical significance was set at $p < .05$, two-tailed. The analysis was approved by the local ethical committee of the University Hospitals Ghent. Research was performed according to the principles of the Declaration of Helsinki.

Results

We included a total of 2037 VLBW infants. Annual mortality rates showed a gradual decrease over the last 20 years from 22.5% in 2000 to 7.9% in 2020. Annual mortality rates up to 2007 varied between 17.5% and 24.5%. Annual mortality rates between 2008 and 2012 varied between 10.6% and 13.7%. Annual mortality rates as of 2013 varied between 6% and 8.8%. As we observed a stepwise reduction in mortality in 2008 ($< 15\%$) and 2013 ($< 10\%$), we decided to divide the entire group in 3 different epochs based on mortality, i.e. epoch 1 (2000–2007) with mortality rates $> 15\%$, epoch 2 (2008–2012) with mortality rates between 10–15% and epoch 3 (2013–2020) with mortality rates $< 10\%$. Inter-epoch significance levels were significant at $p < .00001$ (data not shown).

We observed a decline in mortality in almost all GA, but predominantly in infants with the earliest GA of 24 and 25 weeks (data not shown). A total of 62 infants with life-threatening congenital malformations were identified over the two decades, i.e. 27 in epoch 1, 23 in epoch 2, and 16 in epoch 3. Only 3 had a GA of 24–25 weeks. Trends in mortality remained comparable after exclusion of these infants with life-threatening congenital malformations (data not shown).

Survival without major morbidities almost doubled over time from 25.3% to 47.4% ($p < .00001$).

Comparisons of pre-, peri- and postnatal characteristics, as well as major morbidities were outlined in Table 1. Overall GA and BW were comparable.

Differences between epochs 1 (2000–2007) and 2 (2008–2012) (Table 1)

Significant increase in survival ($p < .001$) was observed. We observed no differences in prenatal characteristics. Most important finding was a significant reduction in outborn infants from 27.8% to 21.3% ($p = .0117$). Postnatal characteristics were similar between the two groups. No increase in major morbidities was observed, on the contrary, there was a significant decline in PDA from 12.3 to 7.7% ($p = .0095$) and IVH

from 18.9 to 10% ($p = .0001$). We observed a reduction of more than 50% of IVH grade III-IV ($p = .0023$) from 9.3% to 4.5%.

Differences between epochs 2 (2008–2012) and 3 (2013–2020) (Table 1)

Increase in survival continued ($p = .0078$), especially in those with a GA of 24 weeks. We observed differences in prenatal characteristics. Ten percent less tocolysis was administered from 70.5 to 61.8% ($p = .0006$). The number of multiple pregnancies decreased from 36.3 to 28.9% ($p = .0037$). Most striking difference in prenatal characteristics was the doubling in the administration of magnesium sulfate from 9.2% to 22.1% ($p < .00001$). Birth characteristics were similar. In the postnatal characteristics, we saw a 10% increase use

Table 1. Comparisons of pre-, peri- and postnatal characteristics, as well as major morbidities and mortality between epochs 1 (2000–2007), 2 (2008–2012) and 3 (2013–2020).

	EPOCH 1 (2000–2007)	EPOCH 2 (2008–2012)	<i>p</i> -value	EPOCH 3 (2013–2020)	<i>p</i> -value
Total number	718	506		822	
Median pma (wks)	29 (27–31)	29 (27–31)	.8457	29 (27–30)	.9217
Median bw (g)	1140 (890–1340)	1155 (925–1347.5)	.5697	1150 (877.5–1329.25)	.5234
PRENATAL CHARACTERISTICS					
Preterm labor	416 (57.9%)	269 (53.1%)	.1097	437 (53.1%)	.9951
Preclampsia	129 (17.9%)	105 (20.7%)	.2517	199 (24.2%)	.1646
Chorioamnionitis	69 (9.6%)	43 (8.4%)	.5728	82 (9.9%)	.4244
Lung maturation	543 (75.6%)	400 (79.0%)	.1822	686 (83.4%)	.0973
Tocolysis	499 (69.4%)	357 (70.5%)	.7685	503 (61.1%)	.0006
Magnesiumsulfate	62 (8.6%)	47 (9.2%)	.7692	180 (20.4%)	<.00001
Multiple pregnancy	248 (34.5%)	184 (36.3%)	.5507	235 (28.5%)	.0037
Primigravida	338 (47.0%)	251 (49.6%)	.4155	380 (43%)	.5243
Spontaneous pregnancy	585 (81.5%)	403 (79.7%)	.4675	690 (83.9%)	.0550
CHARACTERISTICS AT BIRTH					
Sectio caesarea	434 (60.4%)	292 (57.7%)	.3674	518 (63%)	.0616
Outborn	200 (27.8%)	108 (21.3%)	.0117	144 (17.5%)	.0980
Boys	359 (50.0%)	252 (49.8%)	.9919	435 (52.9%)	.2948
POSTNATAL CHARACTERISTICS					
Parenteral nutrition (d)	16 (12–23)	16 (11–24)	.8738	15 (11–21)	.5578
Ventilation (d)	6 (2.75–11)	6 (2–14)	.9326	5 (1–11)	.3082
Surfactant	270 (37.6%)	204 (40.3%)	.3683	424 (51.5%)	.0001
Corticoids	132 (18.3%)	76 (15.0%)	.1426	110 (13.3%)	.4509
Regional transfer	356 (50.0%)	263 (59.1%)	.5341	416 (50.6%)	.6687
MORBIDITY					
Clinical or confirmed late-onset infection	277 (38.5%)	223 (44.0%)	.0805	382 (46.4%)	.4257
PDA	89 (12.3%)	39 (7.7%)	.0095	93 (11.3%)	.04147
NEC	22 (3.0%)	26 (5.1%)	.0907	42 (5.1%)	.9163
IVH any grade	136 (18.9%)	55 (10.0%)	.0001	89 (10.8%)	.9467
IVH grade I-II	76 (10.5%)	34 (6.7%)	.0259	54 (6.5%)	.9945
IVH grade III-IV	67 (9.3%)	23 (4.5%)	.0023	31 (3.7%)	.5818
PVL	120 (16.7%)	104 (20.5%)	.1018	175 (21.2%)	.8022
BPD at 36 weeks	213 (29.6%)	133 (26.2%)	.2190	266 (32.3%)	.0223
Discharge with oxygen	21 (2.9%)	10 (1.9%)	.2983	36 (4.3%)	.0299
ROP	30 (4.1%)	21 (4.1%)	.9036	61 (7.4%)	.0221
MORTALITY					
Mortality	152 (21.1%)	61 (12.0%)	<.0001	62 (7.5%)	.0078
Survival without major morbidities	182 (25.3%)	190 (37.5%)	<.00001	390 (47.4%)	.0005

Values are medians with interquartile range (IQR) or numbers with percentages. Pearson Chi-Square test and one-way ANOVA were used for statistical analysis. The cutoff for statistical significance was set at $p < .05$, two-tailed. *p*-values in bold are statistically significant *p*-values (i.e. $p < .05$, two tailed). G: grams; wks: weeks; d: days; PMA: postmenstrual age; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; BPD: bronchopulmonary disease; ROP: retinopathy of prematurity.

Table 2. Comparisons of pre-, peri- and postnatal characteristics, as well as major morbidities and mortality between epochs 1 (2000–2007), 2 (2008–2012) and 3 (2013–2020) in very low birth weight infants with a gestational age of 24–25 weeks.

	EPOCH 1 (2000–2007)	EPOCH 2 (2008–2012)	<i>p</i> -value	EPOCH 3 (2013–2020)	<i>p</i> -value
Total number	78	47		105	
PRENATAL CHARACTERISTICS					
Preterm labor	68 (87.1%)	40 (85.1%)	.9536	85 (80.9%)	.6967
Preclampsia	2 (2.5%)	1 (2.1%)	.6535	8 (7.6 %)	.3401
Chorioamnionitis	28 (35.8%)	18 (38.2%)	.9377	22 (20.9%)	.0408
Lung maturation	48 (61.5%)	28 (59.5%)	.9770	92 (87.6%)	.0002
Tocolysis	63 (80.7%)	41 (87.2%)	.4905	81 (77.7%)	.2208
Magnesiumsulfate	3 (3.8%)	1 (2.1%)	.9966	21 (20%)	.0081
Multiple pregnancy	26 (33.3%)	11 (23.4%)	.3292	44 (41.9%)	.0443
Primigravida	47 (60.1%)	15 (31.9%)	.0039	42 (40%)	.4410
Spontaneous pregnancy	59 (75.6%)	36 (76.5%)	.9242	77 (73.3%)	.8222
CHARACTERISTICS AT BIRTH					
Sectio caesarea	11 (14.1%)	14 (29.7%)	.0583	41 (39%)	.3599
Outborn	15 (19.2%)	12 (25.5%)	.5452	21 (20%)	.5811
Boys	40 (51.2%)	28 (59.5%)	.4738	62 (59%)	.9064
POSTNATAL CHARACTERISTICS					
Parenteral nutrition (d)	32.5 (27–40.5)	36 (24–48.5)	.5137	26 (12–41.25)	.1137
Ventilation (d)	16.5 (8–23)	20 (5.5–30)	.4664	16 (1.75–30)	.5884
Surfactant	39 (50%)	33 (70.2%)	.0425	83 (79%)	.3282
Corticoids	21 (26.9%)	19 (40.4%)	.1708	49 (46.6%)	.5900
Regional transfer	7 (8.9%)	4 (8.5%)	.8124	14 (13.3%)	.5626
MORBIDITY					
Clinical or confirmed late-onset infection	25 (32%)	27 (57.4%)	.0092	69 (65.7%)	.4268
PDA	16 (20.5%)	9 (19.1%)	.9631	42 (40%)	.0197
NEC	2 (2.5%)	3 (6.3%)	.5590	9 (8.5%)	.8910
IVH any grade	30 (38.4%)	15 (31.9%)	.5848	29 (27.6)	.7291
IVH grade I-II	12 (15.3%)	9 (19.1%)	.7654	15 (14.2%)	.6035
IVH grade III-IV	21 (26.9%)	10 (21.2%)	.6211	14 (13.3%)	.3170
PVL	16 (20.5%)	20 (42.5%)	.0150	37 (35.2%)	.4966
BPD at 36 weeks	30 (38.4%)	29 (61.7%)	.0194	55 (52.3%)	.3725
Discharge with oxygen	0 (0%)	3 (6.3%)	.0510	9 (8.5%)	.8910
ROP	3 (3.8%)	11 (23.4%)	.0021	36 (34.2%)	.2494
MORTALITY					
Mortality	60 (76.9%)	22 (46.8%)	.0012	23 (21.9%)	.0035
Survival without major morbidities	3 (3.8%)	0 (0%)	.2905	11 (10.4%)	.0183

Values are medians with interquartile range (IQR) or numbers with percentages. Pearson Chi-Square test and one-way ANOVA were used for statistical analysis. The cutoff for statistical significance was set at $p < .05$, two-tailed. *p*-values in bold are statistically significant *p*-values (i.e. $p < .05$, two tailed). g: grams; wk: weeks; d: days; PMA: postmenstrual age; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; BPD: bronchopulmonary disease; ROP: retinopathy of prematurity.

of surfactant from 40.3 to 52.1% ($p = .0001$). Other postnatal variables were comparable between epochs. There was a significant increase in chronic respiratory morbidity, i.e. BPD at 36 weeks from 26.2 to 32.7% ($p = .0223$) and discharge home with oxygen from 1.9% to 4.4% ($p = .0299$). We saw approximately doubling the prevalence of ROP from 4.1% to 7.5% ($p = .0221$).

Subanalysis of infants 24–25 weeks (Table 2)

As the most significant decrease in mortality was observed in VLBW with a GA of 24–25 weeks, a sub-analysis was performed in this group ($n = 78$ in epoch 1; $n = 47$ in epoch 2; $n = 105$ in epoch 3). Significant decrease in mortality was observed from 76.9% in epoch 1 over 46.8% in epoch 2 to 21.9% in epoch 3. Most important differences in prenatal characteristics were an increase in mothers with preeclampsia and multiple pregnancies. Chorioamnionitis decreased

significantly. Administration of lung maturation increased by approximately 25%. An important increase in use of magnesium sulfate was observed in epoch 3 up to 20% ($p = .0081$). Cesarean sections doubled over time. The number of outborn infants remained stable at around 20%. Administration of surfactant and postnatal corticosteroids increased over time. All major morbidities –except for IVH– increased in this subpopulation. PDA and ROP continued to rise, but the increase in the other major morbidities tended to stabilize. The number of infants surviving without any major morbidity increased significantly over time up to 10.4%.

Discussion

Benchmarking outcomes in VLBW infants can provide valuable information for clinicians and families dealing with these infants. We described trends in mortality and major morbidities in all VLBW neonates admitted

to the quaternary neonatal intensive care unit in Ghent, Flanders, Belgium over the last 20 years.

Flanders is a region in Belgium with an official guideline about when to resuscitate extreme preterm infants based on GA advising resuscitation from 26 weeks and non-resuscitation below 24 weeks unless parents specifically request resuscitation after being well informed. Between 24 and 25 weeks (= grey zone), decision-making is done case-by-case through shared decision-making between parents and clinicians and considering all relevant factors. This guideline has remained stable over the years however we observe a shift toward more resuscitation in the grey zone [11].

As described in the literature mortality declines in VLBW infants [2–8]. This was confirmed in our cohort with a significant decline in mortality over 3 epochs from 25% to 8%. Decreased mortality was observed in all GA, but predominantly at 24 and 25 weeks. In this subpopulation, mortality decreased from 75% to almost 20%. These trends were also observed by other groups [12,13].

Over the years a lot of (subtle) changes in obstetric and neonatal care have been made in our unit driven by the availability of new knowledge, guidelines from outside the unit, the need for standardization, participation in research, the occurrence of adverse events, and wish to improve care [14]. Over the years, our guidelines have been adapted according to the European Standards of Care for Newborn Health (<http://www.efcni.org>). Even though we observed a stepwise reduction in mortality in 2008 below 15% and in 2013 below 10%, no specific associations could be made directly explaining the reduction in mortality. Decrease can only be explained by a combination of different (subtle) changes over the years.

Obstetric care has been evolving over the last decades [15–20]. Our findings coincided with these changes. We observed more cesarean sections and the use of tocolysis declined. The number of outborn infants significantly declined in our cohort from 27.8% to 17.7% [21,22]. Focus on reducing outborn infants was mainly in epoch 1 when our maternal intensive care unit and NICU were expanded. Given the known association between reduced mortality and birth of VLBW infants in high-level NICU's [21,22], we suggested that the reduction of outborn VLBW infants was an important contributor to the increased survival in our cohort. Nevertheless, this could not be demonstrated in our sub-analysis as the number of outborn infants remained stable at around 20%. Another very important pillar in obstetric care is the use of

antenatal corticosteroids [19]. They are recommended for women at increased risk of preterm birth and are associated with decreased neonatal mortality and morbidity [19]. In our cohort, the use of antenatal corticosteroids steadily increased over time from 75.6% to 84.3%. This increase was even more pronounced in the subgroup of infants 24–25 weeks from 61.5% to 87.6%. A third important observation is the significant increase in antenatal use of magnesium sulfate. Its use more than doubled in epoch 3 and in those below 26 weeks GA, we even observed a more than fivefold increase. Magnesium sulfate is a molecule that plays a key role in treating preeclamptic women and in protecting the immature brain [17]. It is nowadays also recommended for women at risk of imminent preterm birth <32 weeks GA [17,19].

Several changes in neonatal care have been implemented over the years according to what is described in the literature [23–33]. We observed a slight decrease of days on parenteral nutrition and invasive ventilation. Fewer days of parenteral nutrition and invasive ventilation can lead to fewer days of invasive devices. This could have an impact on the number of late-onset infections. However, this could not be demonstrated in our cohort. The use of surfactant has significantly increased to 52.1% in all VLBW infants and to 79% in those 24–25 weeks. Over the years, it has become standard of care that all intubated VLBW infants receive surfactant, preferably prophylactic or early therapeutic. Use of postnatal corticosteroids has declined to 13.5%. The type of postnatal corticosteroids also changed in epoch 3 from dexamethasone to hydrocortisone. The duration of a course of corticoids has also become shorter. Recent insights suggest that hydrocortisone treatment does not result in substantially higher survival without CLD [26]. However, its use remains high and is still increasing in the subgroup of VLBW infants below 26 weeks GA. Changing practices in the treatment of PDA were seen over the years [23,28]. In our unit, the treatment of PDA changed from prophylactic in epoch 1 to therapeutic treatment in epoch 2 to expectative management in epoch 3. New insights into ventilation techniques and optimization of oxygen use have been implemented in our unit. Invasive ventilation techniques have changed from pressure-controlled ventilation to more gentle volume-targeted ventilation. Also, noninvasive ventilation has been ameliorated with better nasal continuous airway positive pressure (nCPAP) and the availability of BiPAP (bilevel positive airway pressure) and heated, humidified, high-flow nasal cannula. Prophylactic caffeine treatment is started in all VLBW

infants. For the prevention of sepsis, catheter bundles have been installed in our unit [33]. Over the years, also the principles of Kangaroo Care and Newborn Individualized Developmental Care and Assessment Program (NIDCAP) have been implemented in our unit [34]. Most of the above-described changes in neonatal care took place in epoch 3.

From our findings, we suggest that increased survival is the result of a complex interplay between obstetric and neonatal care. Important points increased use of antenatal corticosteroids and magnesium sulfate and reduction of outborn infants, as well as a combination of important - sometimes subtle - improvements in several neonatal key domains such as there are nutrition, respiratory care, medications, and central line care. The use of antenatal corticosteroids increased gradually over time due to improved obstetric care, whereas the increased use of magnesium sulfate was a change that took place only in epoch 3. Reduction of outborn infants was an important achievement in epoch 1 and continued to improve in epoch 2. The improvements in neonatal care, such as new ventilation techniques, catheter bundles, and principles of Kangaroo Care and Newborn Individualized Developmental Care and Assessment Program (NIDCAP) are changes in care that were implemented in epoch 3.

Besides the significant decline in mortality, another important finding was the significant decrease in IVH which is seen in our cohort. This finding was also confirmed by other research groups [35]. IVH any grade approximately halved to 10.9%. IVH grade I-II decreased to 6.6%. Most significant decline was observed in IVH grade III-IV from about 1/10 VLBW newborns to less than 1/25 VLBW newborns. IVH III-IV is the most important short-term neurological complication in VLBW infants and is known to be associated with a substantial risk of mortality and long-term neurological sequelae [31]. The incidence of severe IVH is associated with GA [31]. As severe IVH occurs predominantly in VLBW below 29 weeks, reduction in IVH grade III-IV in this population might be an important explanation for increased survival in this subpopulation. Another explanation for the reduction of IVH can be the concomitant decrease in PDA. Presence of PDA has been implicated in the occurrence of IVH due to fluctuation in cerebral blood flow [23,28]. Changing practices in the treatment of PDA, as well as new ventilation techniques might have had an impact on the occurrence of PDA [23,28]. This hypothesis however cannot be sustained in epoch 3 as we observe a further decline in IVH with increasing PDA. The increase

of PDA in epoch 3 is probably attributable to the increased survival of those with the earliest GA as PDA is predominantly present in these infants [23,28]. Only slight increase in PVL was seen in epoch 2 and stabilized in epoch 3 at 21.5%. Thus, despite the increased survival of VLBW infants at the earliest ages of 24 or 25 weeks, PVL stabilized. We even see a decrease in PVL in those 24–25 weeks from epoch 2 to epoch 3. This could be attributable to the increased administration of antenatal magnesium sulfate - especially in epoch 3 - which is known to protect the immature brain. The same conclusion can be drawn regarding stabilization of late-onset infections as previously suggested by our group [36]. NEC increased slightly in epoch 2 but stabilized in epoch 3 at 5.2% comparable to what is found in the literature [32]. BPD at 36 weeks and the number of infants discharged home with oxygen increased significantly, respectively up to 32.7% and 4.4% and up to 52.3% and 8.5% in infants 24–25 weeks. This occurs despite advanced respiratory care with increased use of surfactant, decreased use of postnatal corticosteroids, changes in ventilation practices, and optimization of oxygen targets. The increase in BPD is also observed in other groups [4,8,27]. It remains unclear what contributes to this increase. Despite changed oxygen targets and gentle ventilation practices, a suggested possibility is the sustained need for high levels of respiratory support (fraction of inspired oxygen and ventilation) due to the increased survival [24–26,29,30]. Also due to increased survival of the infants at the earliest GA, we observed an increased incidence of ROP with almost doubling of the numbers. This increase in ROP is also observed by other groups [37,38].

Our design has its limitations as it is a retrospective single-center analysis. Moreover, changes in care have been installed gradually and it is not possible to determine when these changes were exactly installed. Also, no long-term follow-up on our cohort is available. However, the major strengths of this study are its homogenous and longitudinal data. These data were prospectively entered at the time of discharge from the NICU in a national database with all perinatal items entered in the database strictly defined by experts from the Belgian Society of Neonatologist. Moreover, all infants were consecutively entered into the database without any exclusion providing “real life NICU experience”. Our NICU is one of the largest in Belgium. Analysis of our results over the last two decades can be considered as a representation of the national evolution in neonatal intensive care.

Survival in VLBW infants increased significantly over time. This is probably due to a combination of changes in obstetric and neonatal care. The most pronounced increase was seen in those infants at the youngest ages of 24- and 25 weeks. As we observed a shift toward more active treatment in this subgroup, it is important also to observe trends in morbidities. It is important that increased survival is not at the expense of severely increased long-term morbidity. In the last years, we observed an increase in BPD and ROP. These trends will have to be carefully watched in the upcoming years. Large ongoing registries benchmarking outcomes are very important to achieve this. Moreover, they can help guiding caregivers and families dealing with VLBW-infants.

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Data availability statement

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