Short-term outcome of inborn and outborn very low birth weight infants in Belgium. A national survey.
Report of the College of Physicians, Neonatal Section.

International guidelines recommend delivering very low birth weight (VLBW) infants in tertiary centres with sufficient high-risk neonatal activity. The Paediatric Section of the Union of European Medical Specialists and the European Society for Neonatology estimate that the tertiary training centres admit at least 50 VLBW infants per year (January 2007) which is in accordance with the Belgian legislation. The rationale to sustain this policy in the organisation of perinatal care is to admit mothers and babies in hospitals with expertise, sufficient staff and optimal technological equipment. Furthermore newborn transport after birth does not allow optimal treatment during the important period of initial extra-uterine adaptation and induces a stressful mother –infant separation.

The College supported a study group to evaluate the pre and post-natal transfer policy of VLBW infants in Belgium and to analyse mortality and short-term morbidity in the Belgian Nic departments (see text P. Van Reempts et al.). The primary source of the data was the Nicaudit database, which has been elaborated by the neonatologists and substantially developed by the Nic College during the last years. Seventeen out of the 19 official Belgian Nicus sent data for the years 2004 and 2005.
Complementary information was found in the National Minimal Clinical Data set (MKG/RCM). Eighty five % of the VLBW infants registered in the Nicaudit database are born in a tertiary Nicu. Their outcome measures did not show statistical differences compared to the outborn babies. Whether this is a selection bias with only the robust babies being considered candidates for transfer is an unanswered question. Furthermore the outcome of VLBWI who remained in a non Nic department is unknown.
The major finding of this study showed that mortality and short-term morbidity like chronic lung disease, cystic periventricular leukomalacia, infections and length of stay were strongly dependent on the Nicus themselves. Some important morbidities like retinopathy of prematurity could not be thoroughly analysed because of lack of information from the N* units where babies are back transferred after the Nic stay.

Future plans: the College of Neonatology will continue to further analyse and focus on the short-term mortality and morbidity in VLBW infants. Study groups will be organised to verify the individual interpretation of the definition among the different units and try to find out whether the observed differences among Nics persist after correction for interpretation. Registration of the whole neonatal stay (Nic and N*) is mandatory if the resources are to be distributed according to the needs of infants and centres. N* units without local Nic will be involved in the registration of items in this vulnerable population. In the future long term outcome variables should be linked with the Nicaudit dataset.

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Monday, 09 February 2009

The effect of being born in a tertiary center versus being outborn on short term outcome of VLBW admitted to one of the NICU's in Belgium

The College of Physicians of Mother and Newborn, Newborn section,
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Aim of the report

In 2006 the Newborn section of this College choose to evaluate the outcome of neonates with a birth weight less than 1500 gram primarily in relation to his or her origin/place of delivery, and this for the years 2004 and 2005 using the NICaudit database as the main source of analysis. The hypothesis being that infants born in a perinatal centre either after antenatal or in utero transfer (both further called in utero transfers or IUTR) or born in a perinatal centre where the mother was booked to deliver (further called inborns or IB) have lower mortality and morbidity at discharge from the NCU than infants transferred after birth to a tertiary neonatal unit (further outborns or OB).

Introduction

The concept of in utero – and antenatal transfer to a regional perinatal center was introduced in the UK in 1948 by D. Baird, [8].However, it was first implemented in North America and Canada during the 70ies and further elaborated in the 80 and 90ies (ref 57-59). The main goals were the early detection of high-risk pregnancies to allow timely delivery in hospitals organised to provide optimal perinatal care, including expertise, sufficient staff, equipment and technology [76] [77] [78]and on the other hand to to provide timely transport to a perinatal centre of high-risk infants not detected during the antenatal period .This system of perinatal care existed of three levels of maternity units, transport services to the different levels, and continued education. These levels in the USA were redefined recently into basic care (level I), specialty care (level II) and subspecialty care (level III) [3]and [66].
One of the aims was the encouragement of in utero transfer of the at risk fetus to a tertiary care center. Based on a large scientific literature it now is generally agreed that in most cases the prognosis for very preterm babies is better when they are born in units providing on-site neonatal intensive care, also

designated as level III units, and therefore that preterm babies with a gestational age less than 32 weeks, should be delivered in hospitals with an on-site neonatal unit capable of providing full intensive care [3;4;5;6;7;8;9;11;12;13] [64], [12], [77]. [57;72]The American Academy of Pediatrics recommends that deliveries occurring before 32 weeks of gestation take place in such specialized units, [4]. In the state of Victoria, Australia, fewer than 10% of ELBW (GA less than 28 weeks) infants are born outside level III perinatal centres, while proportionally more ELBW infants are being offered intensive care over time [18] [58] and most birth <33 weeks deliver in perinatal centres.

In Europe the implementation of perinatal care was introduced more slowly in the nineties, but many European countries have since passed laws or issued recommendations [16], [9] The proportion of very preterm babies delivered in maternity units with on-site intensive care has been proposed as a quality-of-care indicator of perinatal health systems across Europe [79].

The Nordic European countries have developed validated quality indicators for in utero and neonatal transfers[36]. In France the policy was implemented in 1998 [42], in Poland in 1995 [55]and in Belgium in 1996 [40]. Both the Dutch [25] and the Italian [48] recommendations were issued in 1997.

Studies find better outcomes, including low mortality rates, for very preterm newborns in larger, more specialized units [75] [13;22;53;60;61]. Also recently Phibbs reported that high volume high level neonatal units showed less in-hospital mortality than low volume low level neonatal units, although only 25% of the neonates appeared to be born in maternity units with high level high volume neonatal units [52]. However, there are reports showing that delivery and hospitalization in small units can lead to similar outcomes [5;7;21;39;62]. The discussion whether optimal care can be provided in smaller units or outside of tertiary units is relevant since there is a growing trend in many countries towards deregionalization of perinatal care [30;74] [52;70] [10] [12] [23]. In the USA, regardless of the evidence supporting delivery of VLBWI at tertiary centers, a lower percentage is delivered at those centers than the goal of 90% set by Healthy People 2010 [17;63].

In the Europet study, covering 18 regions in 17 European countries, including Belgium, the rate of babies less than 32 weeks GA born in maternities with an on-site large NICU, defined as a unit with more than 40 preterm admissions per year, ranged from 50.8% in France to 97.9 % in Finland. For Belgium this rate was 77.4%. This inborn rate included also the IUTR rate [16]. Recently another European study, MOSAIC (QLG4-CT-2001-01907), assessing models of access of premature neonates less than 32 weeks gestational age to neonatal intensive care in 10 European regions, showed for

Flanders a 44.5 % maternal transfer rate during pregnancy to a perinatal center of which 30.8 % and 13.7% respectively originated from a previous hospitalisation in a regional maternity hospital (in utero transfer) or were directly transferred without previous hospitalisation (antenatal transfer). 82% of live births with a gestational age less than 32 weeks and admitted to neonatal intensive care occurred in a maternity with a Perinatal Center P*, meaning that many mothers were already followed in this center and thus never were transferred extra-utero.

Although prenatal transfer of the mother to a perinatal center is preferred, structural factors such as shortage of NICU cots and management factors may impede maternal transfers. In the UK, for example, the number of transfers between level III units is increasing due to lack of space [47]. These problems also exist in The Netherlands: The authors of a Dutch governmental report concluded that 983 mothers whose babies needed intensive care were not admitted to a perinatal centre before delivery [25].

And although in some cases transport after birth does not seem to increase the risks of mortality[5;6;7] [21;39] [53] [69], a study of high-risk infants in Scotland and Australia concluded that observed differences in mortality were due to differences in the characteristics of neonatal units [38;43]. On the other hand as many VLBW infants are delivered in high care facilities it seems that also NICU characteristics, become important determinants of neonatal morbidity [67] [37].

In Belgium, levels of perinatal care were outlined in 1996 by the Government. The Royal Decree specifies general provisions and architectonic, functional and organisational standards for the M-service[1], the N*-function[2], the NIC-service and the P*-function[3] (MIC[4] and NIC[5]) [40].

In contrast to international standards where 3 levels of neonatal care are commonly accepted, two levels of perinatal care exist , i.e. one level, consisting of the M service, providing normal care of the mother and the N* function, providing normal and specialized care of the neonate. A second level, including maternal and neonatal intensive care, respectively called MIC and NIC, corresponds to the internationally accepted Level III maternal or neonatal intensive care units. However this level in Belgium includes the international Level II services. When both MIC and NIC exist on the same site they may form a perinatal centre (Regional Perinatal Care Function, P*). To be recognised as a MIC, NIC or P* these units are required to adhere to specific criteria as to their organisation and structure,

[1] Maternity
[2] Function of neonatal care
[3] Function of regional perinatal care
[4] Maternal Intensive Care
[5] Neonatal Intensive Care

functioning, staffing. The criteria originate from the federal Health Ministry while their implementation belongs to the authority of the Communities [40]. Although a list of recommendations is given on fetal and newborn high-risk situations for which the presence of a pediatrician needs to be organised at the time of the delivery no specific recommendations are given for in utero transfer or a gestational age or birth weight below which the transfer of the fetus or newborn to a P* is indicated. On the other hand written conventions between the referring hospitals and P*centres need to include criteria for prenatal maternal and postnatal newborn transfer and also retransfer.

In Belgium, except for its participation in the above mentioned European studies, data on IUTR are systematically collected as from…. when the formal registration of the birth certificate included IUTR . Since 1985 the Belgian Society of Neonatology collects basic neonatal data, including IUTR, on a voluntary basis from all NICU's in Belgium for statistical purposes. However these data are confidential. At the federal level, the College of Physicians for Intensive Neonatal Care, created by Royal Decree in February 1999, further enlarged into a College of Physicians of the Mother and Newborn with a Maternal and a Newborn section in 2003, developed a national neonatal database (NICaudit) as a quality assessment tool: an audit program for all Belgian NICU's [41]. In this database 40 neonatal data items from all neonates admitted to neonatal intensive care units (NICU) in Belgium are systematically entered on a voluntary basis [14]This College reported in 2004 5348 admissions from 16 NICU's with an IUTR rate of 16.7% (N= 891). 402 out of 913 neonates with a birth weight less than 1500 gram in 17 NICU's were IUTR (44%). In 2005 a total of 5669 admissions in 16 NICU's were recorded with an IUTR rate of 15.2% (N=867). 459 (44.7%) out of 1028 with a birth weight less than 1500 gram in 18 NICU's were IUTR. (PS: some NICU's only enter neonates <1500 gram birth weight in the database). This database serves as the main data source for the present report.
At the regional level, IUTR was recorded temporarily in Flanders between 1989 and 1995: during this period the IUTR rate for GA <32 weeks increased from 20% to 65 %.Unfortunately no further registration was performed in the following years. A one perinatal centre study [24] compared the outcome of 416 neonates from 328 deliveries after in utero transport to 187 neonates transported postnatally (neonatal transport group). Placental abruption was more frequent in the mothers of the neonatal transport group (13 vs. 5%, P=0.001) and prenatal corticosteroids were administered significantly less (67 vs. 13%, P<0.0001). Preterm rupture of the membranes (36 vs. 20%, P<0.0001), preterm labour (73 vs. 36%, P<0.0001), and pre-eclampsia (10 vs. 7%, P<0.0001) were more frequent

in the in utero transport group and this group had a lower mean birthweight and gestational age. There was no significant difference for overall neonatal mortality, respiratory distress syndrome, intraventricular hemorrhage, necrotising enterocolitis, persisting ductus arteriosus or septicaemia. These data are in accordance with recent findings in the Flanders' part of the MOSAIC study [28].

Methods

1. Population:

Data sources:

- The national NICaudit database of the Newborn section of the College of Physicians of the Mother and Newborn served as the primary data source [41]. From the 192 items which can be entered in this database for every neonate admitted to a NICU, 40 items were selected, for which all NICU's agreed to deliver yearly complete data. The aggregated anonymous data can be accessed by privileged password through a specific website (www.colnic.be). One of these items concerns the origin of the neonate, i.e. whether being inborn, outborn, or the result of IUTR.
- The National Minimal Clinical Data set (MCD) ((MKG/RCM data)) (source: Federal Public Service, Health, Food Chain Safety and Environment).
  This data set served as a secondary source to calculate the total number of births and births at maternities without a MIC/NIC and those with a MIC/NIC.

  Inclusion criteria:
  All live birth neonates with a birth weight less than 1500 gram admitted to an NICU in Belgium in 2004 and 2005 and registered in the NICaudit database of the Newborn section of the College of Physicians of the Mother and Newborn.
  Exclusion criteria:
  Babies admitted to an NICU later than 10 days after birth, N= 84: as the reason for transfer to a NIC was not related to perinatal events necessitating a particular type of transfer, ie IUTR or postnatal transport
  Babies without defined gender, N=1.
  As such a total of 1845 infants were available for analysis.
  Variables:

Of 40 neonatal categorical or numeric variables 32 were analysed (for a complete list of all 40 items see appendix: retained variables are indicated as " *"). Some variables , e.g. for birth weight, gestational age, days ventilated, days on CPAP, days on oxygen were categorized, such as resuscitation and CLD (see appendix).

Statisitics:

Descriptive and logistic regression analysis

As the "origin" of the newborn was always the point of particular interest, we first examined a possible association between an explanatory variable and origin testing in two-way contingency tables using classical chi-squared tests [1]. They are presented as cross-tabulations showing column and row percentages in addition to the raw data.

Subsequently the association between the variables of interest and a number of explanatory variables was investigated. Since these variables were categorical we used (binomial) logistic regression (in case of a binomial response variable) and multinomial logistic regression(in case of a multinomial response variable such as ROP) [28;29].

To account for correlation of data (newborns in the same unit) rescaling techniques are used [2].

Ethical approval:

All the Colleges of Physicians in Belgium [41] have the duty to propose quality indicators and criteria to test them, to provide a digitalised registration system, to carry audits on the registered data and to provide an annual national report. All data were anonymous and coded as to their origin of person and origin of NICU. Therefore an ethical approval was not deemed necessary.

Results

The annual hospital statistics for Belgium report a total number of **237 981** deliveries in 2004 and 2005 combined with respectively 33 713 and 34 460 deliveries in hospitals with an NICU (N = 19 in 2004 and 2005) and respectively 84 277 and 85 531 in hospitals (N = 91) without an NIC.

Table 1: Number of deliveries in 2004 and 2005 in hospitals with and without a NIC

	Number of deliveries 2004	Number of deliveries 2005
Hospital with NIC	**33 713**	**34 460**
Hospital without NIC	**84 277**	**85 531**
Total	**117 990**	**119 991**

The number of live born neonates registered with a birth weight <1500 grams in 2004 and 2005 in Belgium was 250 and 227 respectively for hospitals without a NIC. and 765 (287 IUT+478 IB) and 822 (283IUT+539IB) respectively born alive in a hospital with a NIC . Of the 250 and 227 neonates <1500g born in a hospital without NIC, 155 (2004) and 103 (2005), i.e. a total of 258 were transferred to a NIC service.

The NICaudit database reports a total of 10 862 neonates admitted to 16 NIC's in 2004 and 2005 combined.

The total number of neonates with a birth weight <1500 gram admitted to 17 NIC's was 1930.

In this database 265 neonates were reported as outborn.

After applying the inclusion and exclusion criteria, 1845 neonates with a birth weight less than 1500 gram admitted to 17 NICU's were included in the analysis.

1. Descriptive:

Univariate analyses

Eighty six percent (85,6%) of the neonates <1500 gram admitted to an NICU were born in a maternity unit with an NICU, of which 39,6% were inborns (IB) and 46,1% in utero transfers (IUTR). Fourteen percent (14,4 %) were born in a hospital without an NICU and were transferred to a NICU (outborn: OB) (table 4).

However for each GA category less than 29 weeks, between 28% and 35 % were inborns, more than 50% were IUTR transfers and between 9,3% to 14% were outborns. This was also for the BW categories 2 (>500 and < 750 gram) and 3 (>750 and <1000 gram).

For each birth weight category less than 1000 gram, 37 to 50% were inborns, 44 to 56 % were IUTR and between 6.3 to 8% were outborns (table..)

Table 2: Gestational age (in %) in VLBWI versus origin

	N	23-24 w	25 w	26 w	27 w	28 w	> 28w
Inborn	730	1,9	4,7	7,5	11,9	12,9	61,1
AT/IUT	850	2,9	7,4	9,2	12,8	16,1	51,5
Outborn	265	4,2	3,8	7,2	7,6	13,6	63,8

Figure 1: Gestational age (in %) in VLBWI versus origin

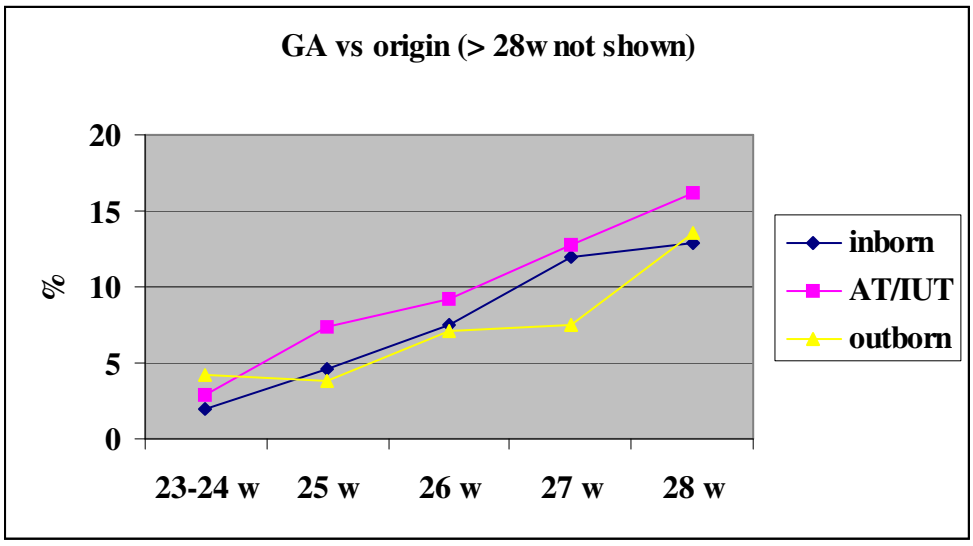
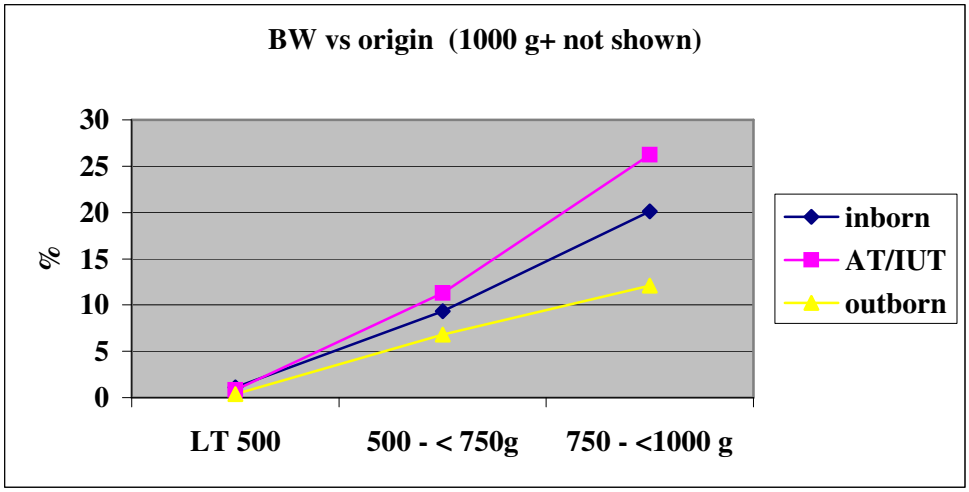


Table 3: Birth weight (in %) versus origin

	N	LT 500	500 - < 750g	750 - <1000 g	GE 1000
inborn	730	1,1	9,3	20,1	69,5
AT/IUT	850	0,8	11,3	26,2	61,7
outborn	265	0,4	6,8	12,1	80,8

Figure 2: Birth weight (in %) versus origin



1.1. Mortality and morbidity

Overall mortality and morbidity according to origin, i.e. inborn, IUTR or outborn, is presented in the following summary table

IB showed significantly higher GA, higher BW, more CLD in survivors, less neonates with oxygen need at 28 days, less neonates needing ventilation but more receiving CPAP, than IUTR (all $p<0.05$).

IB showed a significantly lower BW than OB as well as a lower number of males, more IUGR and more CLD neonates.

IUTR showed a significantly lower gestational age and birth weight, more neonates needing oxygen at 28 days, less needing ventilation, more received CPAP than OB.

Table 4: Main demographic, pathological and therapeutic characteristics of the VLBW neonates

	INBORN **N= 730 (39.6%)**	**IUTR** **N=850 (46.1%)**	**OUTBORN** **N=265 (14.4%)**	**ALL** **N=1845**
GA wks mean +/-SD Median (Rrange)	29,4+/-2,7* 29 (23-37)*	28,8+/-2,6** 29 (23-36)**	29,4 +/-2,8 29 (24-40)	29.1 +/-2.7 29 (23-40)
BW gr mean +/-SD Median (range)	1143+/272 1200 (270-1495) */***	1097+/-273 1100 (320-1499)**	1197+/-237 1250 (396-1498)	1129 +/-27 1180 (270
Gender n (% male)	343 (47)*	429 (50.5)	148(55.8)	920 (49.9)
Multiples n (%)	261 (35.8)***	273 (32.1)**	61 (23)	595 (32.2)
IUGR n (%)	179 (24.5) */***	163 (19.2)	48 (18.1)	390 (21.2)
Congenital Anomaly (lethal or chromosomal anomaly) n(%)	53 (7.3)	63 (7.4)	20 (7.5)	136 (7.4)
Mortality overall n (%)	87 (11,9)	123 (14,5)	37 (14)	247 (13,4)
Early neonatal mortality n (%)	55 (7,5)	79 (9,3)	26 (9,8)	160 (8.7)
Late neonatal mortality n (%)	23 (3,4)	30 (3,9)	9 (3,8)	62 (3.7)
Postneonatal mortality n (%)	9 (1,4)	14 (1,9)	2 (0,9)	25 (1.5)
RDS n (%)	455 (62.3)	532 (62.6)	166 (62.6)	1153 (62.5
CLD % of survivors (n=1596)(%)	160 (24.9)*/**	145 (20.)	34 (15)	339 (21.2)
IVH grade 3 or 4 n (%)	44 (6)	68 (8)	27 (10.2)	139 (7.5)
Cystic PVL n (%)	22 (3)	22 (2.6)	9 (3.4)	53 (2.9)
ROP all/surv n (%)	18 (2.5)/ 18 (2.8)	26 (3.1)/ 26 (3.6)	5 (1.9)/ 5 (2.2)	49 (2.7)/ 4
PN infection n (%)	108 (16.0)	117 (16.0)	40 (16.5)	265 (16.1)
Nosocom infection n (%)	177 (26.1)	193 (26.4)	50 (20.6)	420 (24.4)
NEC/IP n (%)	62 (8.5)	63 (7.4)	19 (7.2)	144 (7.8)
PDA surgery/medical n (%)	34 (4.7)/147 (20.1)	43 (5.1)/161 (18.9)	8 (3.0)/48 (18.1)	85 (4.6)/35 (19.3)
Oxygen at 28 days all/surv n	149 (20.4)*/ 142 (22.1)*	231 (27.2)**/ 218	40 (15.1) /38	420 (22.8)

(%)		(30.0)**	(16.7)	390 (24.9)
Need for ventilation n (%)	368 (50.4)*/***	483 (56.8)**	170 (64.2)	1021 (55.3
Need for nasal CPAP n (%)	466 (63.8)***	514 (60.5)**	139 (52.5)	1119 (60.7
Lenght of stay mean (SD) surv	63 (31)*/***	56 (37)**	46 (34)	57(35)

[1] Perinatal and nosocomial infection without NIC 4 ; * Significant ($p<0.05$) difference between Inborn versus IUTR ; *** Significant ($p<0.05$) difference between inborn versus outborn; ** significant ($p<0.05$) between IUTR versus outborn

Gender

There were significantly less boys in the inborn group than in the outborn ($p=0.04$) but a significant gender difference between the IUTR and outborn groups could not be established.

IUGR

More neonates with a birth weight less than the 10^{th} centile were noted in the inborn group (25 %) than in the IUTR- (19 %) or outborn group (18%) (table detail see appendix). Also significant differences were noted between NICU's. (data not shown).

High order births

32% of the admissions were the result of parts of multiple, especially twin pregnancies (28 %)
Of the twins 11.5% were outborn while 1.4%, resulting from a higher order pregnancy, were outborn.

Congenital anomalies

116 neonates with a major congenital anomaly were born in a tertiary maternity unit versus 20 which were outborns. 1 (12.5%) out of 8 and 19 out of 128 (14.8%) of the newborns with respectively a chromosomal or non-chromosomal major congenital anomaly were outborns.

Mortality: early, late and postneonatal:

From the 1845 admitted neonates 247 (13.4%) died before discharge, 160 (8.7%) in the early-, 62 out 1685 (3.7%) in the late- and 25 out of 1623 (1.5%) in the post neonatal period.

Across type of origin no significant differences were noted for early, late or postneonatal mortality: inborn – IUTR- and outborn rate were: 11,9 %, 14,5 % and 14% respectively. Nor for overall mortality nor for early, late or postneonatal mortality were any significant differences noted in GA-cat or BW-cat (data not shown) according to type of origin.

Significant differences in total mortality before discharge were noted between the NICU's.(overall $p<0.002$) (fig.. and …)

Mortality by GA cat en BW cat

Table 5. Mortality by age and weight (expressed in %).

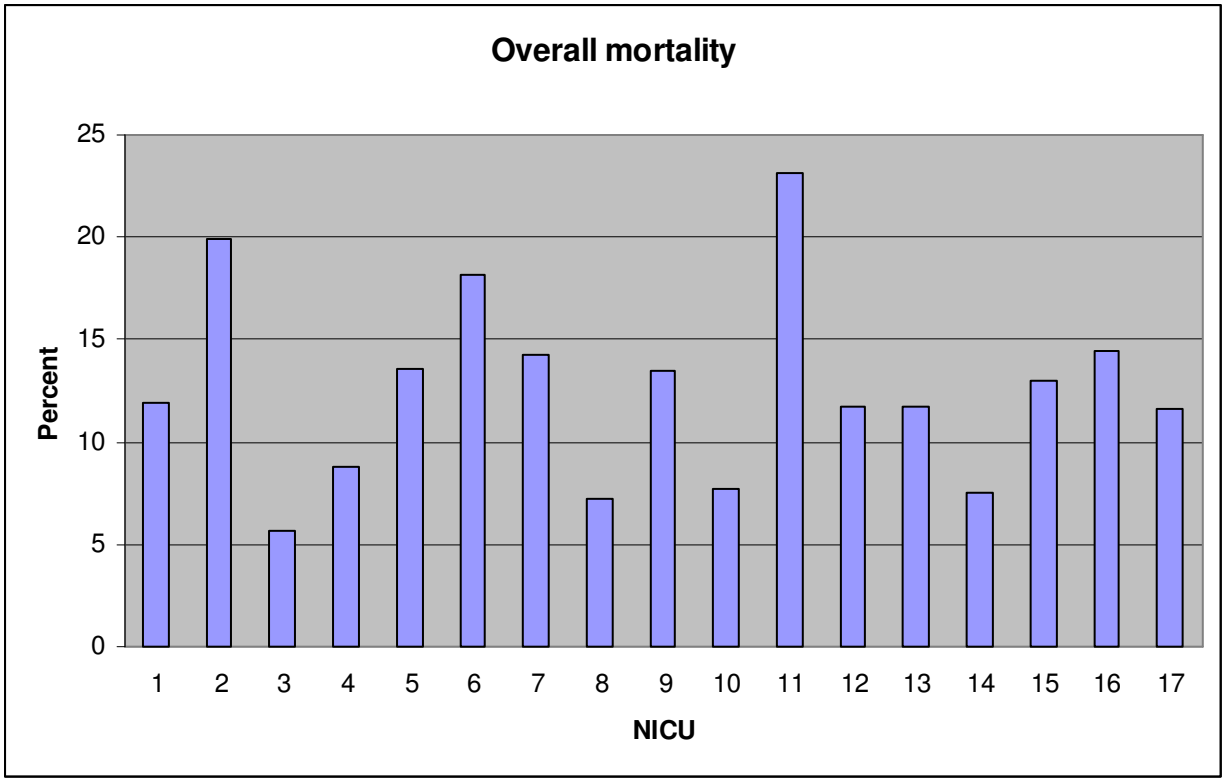
	<500g	**500-749g**	**750-999**	**≥ 1000 g**
<25 w	-	71,43 (55,20;83,77)	57,14 (20,24;88,19)	0,00 (0,00; 94,54)
25 w	80,00 (29,88;98,95)	52,63 (63,05;68,69)	44,07 (31,38;57,53)	40,00 (7,26;82,96)
26 w	80,00 (29,88;98,95)	42,11 (26,72;59,06)	24,14 (15,88;34,72)	31,82 (14,73;54,88)
27 w	75,00 (21,94;98,68)	36,67 (20,54;56,09)	15,05 (8,77;24,13)	22,47 (14,58;32,79)
28 w	-	9,52 (1,67;31,83)	5,17 (1,35;15,30)	13,30 (8,95;19,19)
>28 w	0,00 (0,00;80,21)	15,38 (2,71;46,34)-	5,10 (1,89;12,06)	2,98 (2,03; 4,33)

( ): 95% confidence interval

Table 6. Mortality by age and weight, cases/total

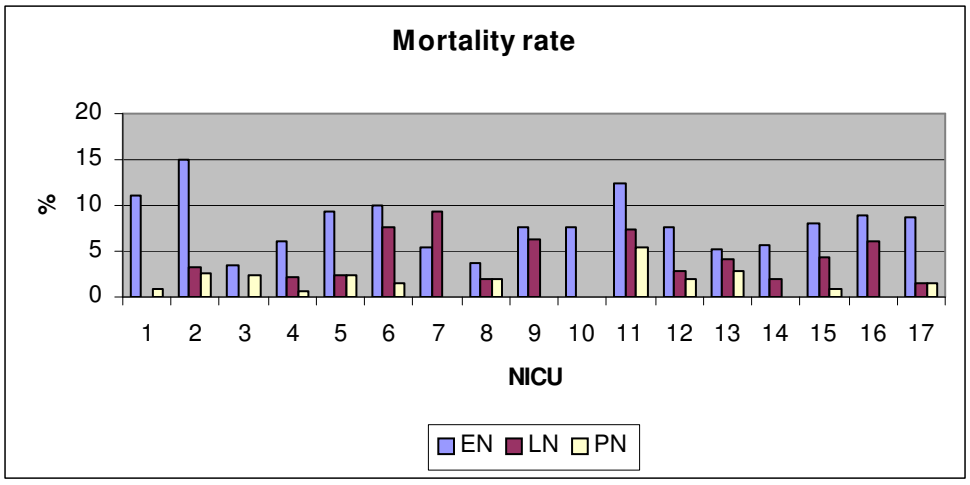
	<500g	**500-749g**	**750-999**	**≥ 1000 g**
< 25 w	-	30/42	4/7	0/1
25 w	4/5	20/38	26/59	2/5
26 w	4/5	16/38	21/87	7/22
27 w	3/4	11/30	14/93	20/89
28 w	-	2/21	3/58	25/188
> 28 w	0/2	2/13	5/89	28/940

Fig 3. Overall mortality in 17 NICU's



p=0.002

Fig. 4. : Early neonatal, Late neonatal and post-neonatal mortality rates, by NICU.



Morbidity

For most variables there were significant differences between NICU's.

Apgar' at 5 minutes for outborns (mean 7.2, SD +/-2.2) was lower than for inborns (mean 8.3, SD+/-1.3) ($p<0.0001$) and IUTR (mean 8.1, SD +/-1.7) ($p<0.0001$). No difference was noted between inborns and IUTR. This remained so for neonates with a GA less than 29 weeks (data not shown). No major differences across type of origin were noted for Apgar scores less than 6 (data not shown).

Significantly more outborns received endotracheal intubation and cardiac compression than inborns or IUTR, and the latter more than the inborns. ($p<0.00$)

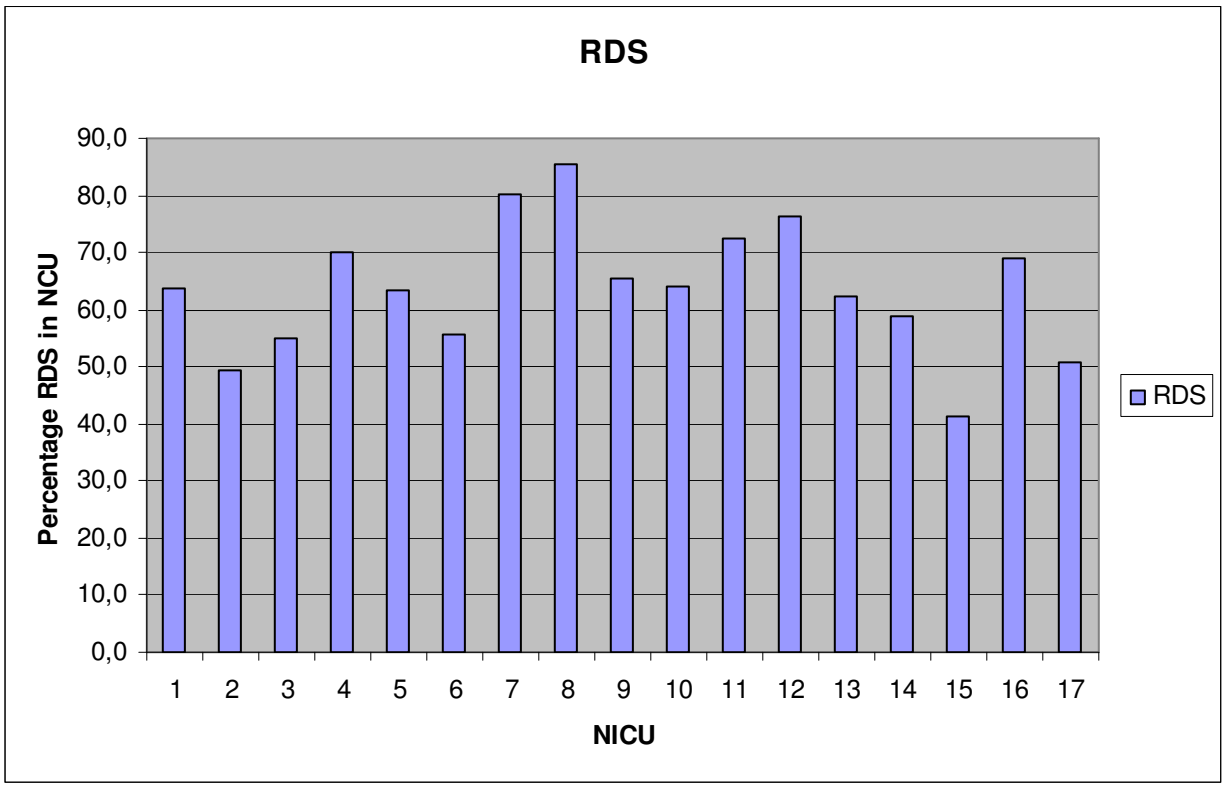
Table 7. orig * ETrea Crosstabulation

	OR	*SE*	*Alpha*	*Confidence Limits*		*Chi-Square*	*Pr > ChiSq*
Inborn vs AT/IUT	0,4955	0,0569	0,05	(0,3956;	0,6206)	37,36	<.0001
Inborn vs outborn	0,3233	0,0496	0,05	(0,2394;	0,4366)	54,22	<.0001
AT/IUT vs outborn	0,6525	0,0936	0,05	(0,4925;	0,8644)	8,85	0,0029

Respiratory outcome

Overall 62,5% of the neonates developed **RDS**. No differences in RDS were noted between inborn, IUTR and outborns. Large differences were noted between NICU's ($p<0.0001$) (Fig 5.)

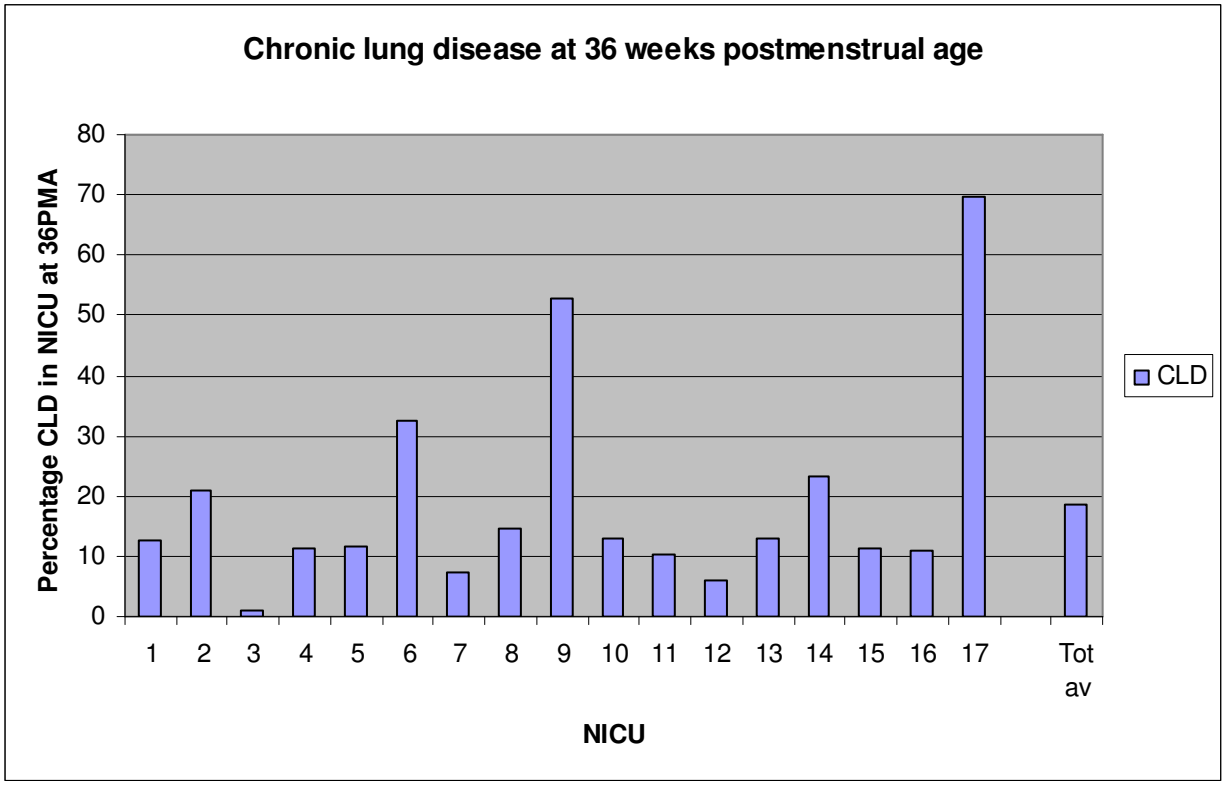
Fig.5. RDS in 17 NICU's



CLD at 36wks in survivors

Of the 1596 survivors at 36 weeks PMA more inborns (25%) and IUTR (20%) developed CLD at 36 weeks than outborns (15%) ($p=0.004$) (Inborns: $p=0.002$; IUTR: $p=0.03$). Large differences were noted between NICU's (fig.6.)($p=0.002$). Significantly more neonates of the combined group of inborns and IUTR showed CLD at 36 weeks PMA than outborns ($p<0.05$, data not shown). This difference disappeared when only neonates with a GA less than 29 weeks were considered.

Fig. 6.Chronic lung disease at 36 weels postmenstrual age



Need of extra oxygen at 28 days

On the other hand significantly more IUTR infants (27 %) needed oxygen longer than 28 postnatal days than inborns (20%) or outborns (15%) (P=0.000). Large differences were noted between NICU's ($p<0.000$) (data not shown). On the other hand when combining inborns and IUTR more neonates of this group needed oxygen for monger than 28 days ()<0.05, data not shown).

IPPV

Overall 64% of the outborns, 57% of the IUTR and 50% of the inborns needed ventilation. Within category 2 (IPPV > 24 hrs - 7 days) more IUTR (45 %) than inborns (35 %) than outborns (20%) were ventilated. ($p=0.001$).). Large differences were noted between NICU's ($p=0.000$)(data not shown)

CPAP

More inborns (64%) than IUTR (60%) than outborns (53%) needed CPAP (p=0.001). No difference was noted between inborns and IUTR. Large differences were noted between NICU's (p<0.000) (data not shown)

Neurological outcome

IVH>3-4

There was a borderline significant trend (p=0.02) for less IB (6%) developing severe IVH than IUTR (8%) and outborns (10,2%) (p=0.07)). No differences were noted between NICU's (p=0.13)(data not shown)

While 3% of the neonates developed **cystic periventricular leukomalacia**, no significant differences were seen between inborns, outborns or IUTR. (p=0.76).). Large differences were noted between NICU's (p<0.03) (data not shown).

Infection

One NIC was omitted from the analysis because of coding problems.

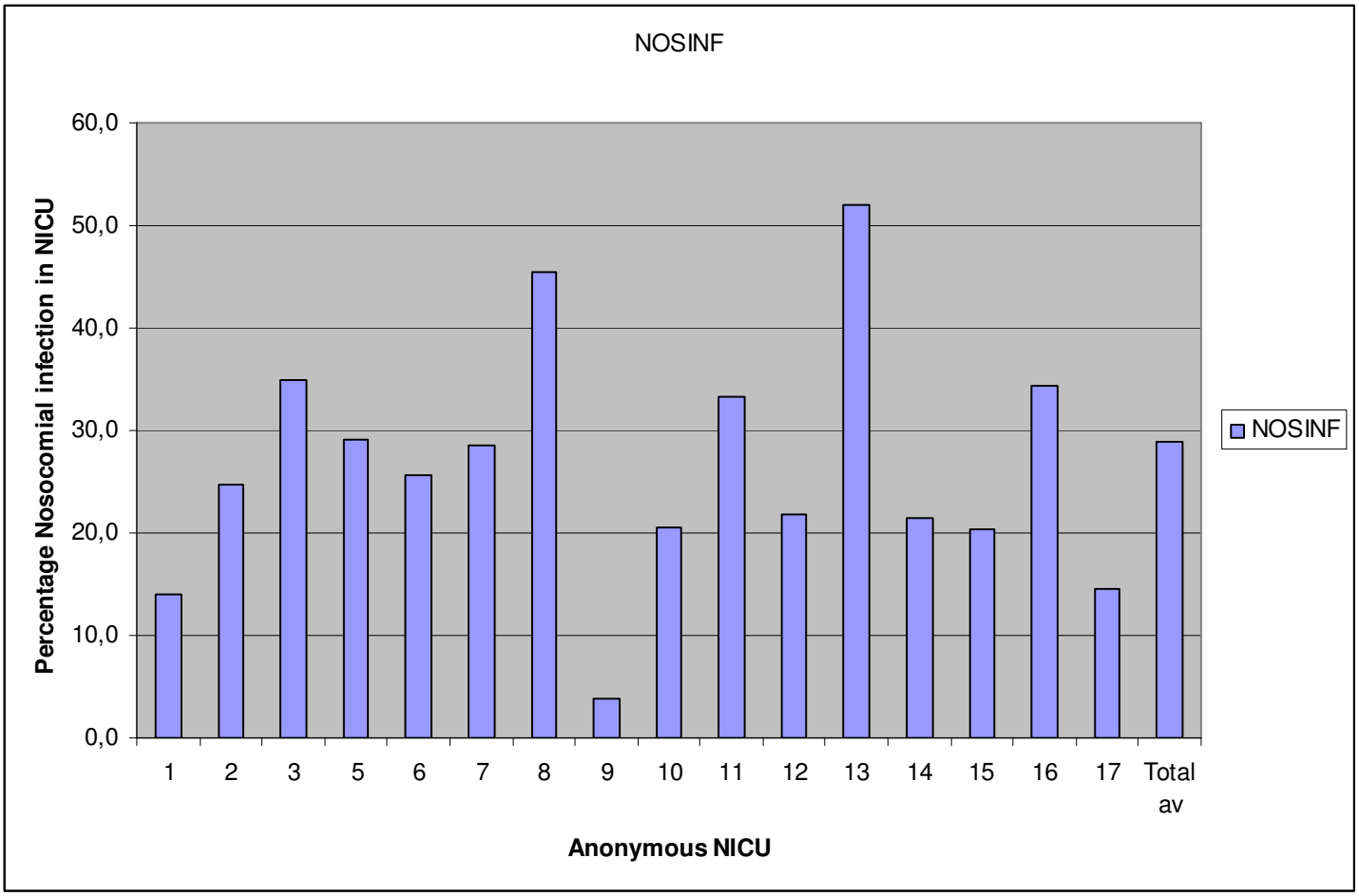
Perinatal infection (without unit 4)

Overall 16% of the infants suffered a perinatal infection; however no differences were noted between any of the 3 groups.). Large differences were noted between NICU's (p<0.000) (data not shown).

Nosocomial infection (without unit 4)

Although there was a trend for less nosocomial infections in the outborn group (21 %), 26 % of neonates in each of the inborn and IUTR group showed nosocomial infections, however no significant differences between the 3 groups could be found. Large differences were noted between NICU's (p<0.000) (fig.7).

Fig. 7. Nosocomial infection in 16 NICU's



*NICU unit 4 omitted

Necrotising enterocolitis (NEC) and isolated perforation (IP)

Between 7.2% and 8.5% of all admissions suffered NEC or intestinal perforation of the gut. No differences between the types of origin could be found. Large differences were noted between NICU's ($p<0.002$) (data not shown).

PDA

Surgical ligation was performed for 5% of the neonates and fluid restriction, diuretics or NSAID's were prescribed for 19% in case of a significant PDA. No differences were found between the types of origin. Large differences were noted between NICU's ($p<0.000$).

ROP

13,2 % of all inborns or 5% of the inborn survivors, and respectively 15,6 % or 9% of the IUTR, and 24,5 % or 21% of the outborns were **not tested** for ROP before discharge from the NICU.
For the survivors less than 29 weeks 1,9%, 3% and 10% of respectively inborn-, IUTR- and outborn survivors were not tested before discharge. This made accurate assessment of ROP not possible, although it seemed that (significantly) fewer outborns developed $\geq$ 3 ROP.

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Length of stay (LOS)

Inborns show a significantly longer LOS stay (mean 63 days; SD+/- 31) than IUTR (mean 56 days; SD+/-37) and Outborns (mean 45 days, SD+/- 35) ($p<0.001$). Also IUTR showed a longer LOS than outborns ($p<0.001$). Large differences were noted between NICU's ($p<0.000$).

2. Multivariable analysis

As there exists much co-linearity between many of the independent outcome variables therefore mainly GA-cat , BW-cat, origin, NIC, gender, multiple pregnancy were entered in the logistic regression models.

Mortality

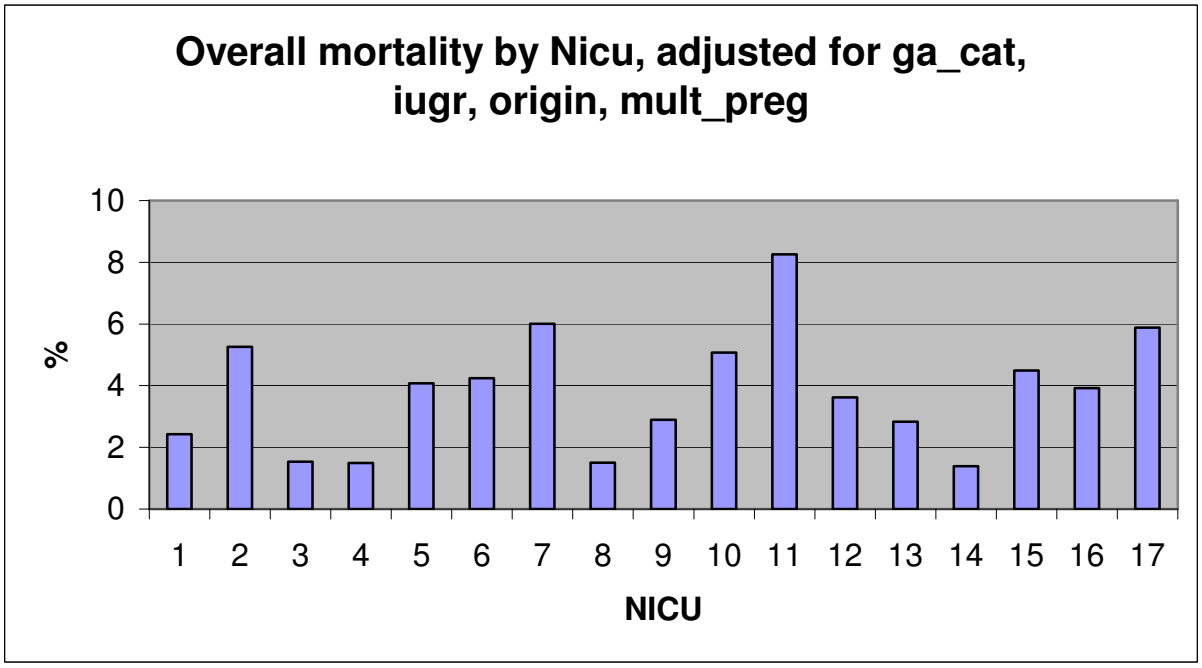
We could not demonstrate a significant difference in overall, early- late and postneonatal mortality according to origin when corrected for GA-cat, BW-cat, IUGR and multiple pregnancy. Due to the small numbers the analysis of late and especially post-neonatal mortality, one has to be very cautious when interpreting the results of our multivariable models. Two types of analyses were carried out including either gestational age groups (upper part of the table) or birth weight (lower part of the table).

Table 8. : overall- early-, late and postnatal mortality by GA and by BW

	Overall				*Early neonatal*				*Late neonatal*				*Post neonatal*		
	OR°	LB°	UB°	P°	OR	LB	UB	P	OR	LB	UB	P	OR	LB	UB
23-24 w	70,4	31,9	155	<.0001	58,6	28,7	120	<.0001	36,1	11,4	115	<.0001	89,7	3,85	2091
25 w	32,2	17,8	58,2	<.0001	20,2	11,1	36,8	<.0001	20,7	8,52	50,1	<.0001	220	21,2	2284
26 w	14,5	8,32	25,1	<.0001	12,2	6,88	21,7	<.0001	9,92	4,14	23,7	<.0001	63,6	6,06	668
27 w	9,62	5,6	16,5	<.0001	7,36	4,1	13,2	<.0001	11,1	5,01	24,7	<.0001	28,2	2,46	324
28 w	4,31	2,4	7,76	<.0001	3,16	1,62	6,14	0,0007	4,96	2,08	11,8	0,0003	20,3	1,77	233
28 w +	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1
Iugr +	1,91	1,23	2,98	0,0041	1,72	1,09	2,72	0,0208	2,05	1,09	3,86	0,0269	2,31	0,71	7,56
Iugr -	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1
Inborn	0,75	0,44	1,29	0,297	0,67	0,39	1,18	0,1665	0,8	0,36	1,76	0,572	1,56	0,27	9,06
AT/IUT	0,76	0,45	1,27	0,2937	0,7	0,41	1,2	0,1936	0,75	0,35	1,61	0,4641	1,38	0,25	7,46
Outborn	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1
> 2	1,3	0,6	2,83	0,5033	1,88	0,91	3,9	0,0881	0,95	0,28	3,21	0,9386			
Twin	0,66	0,43	1,01	0,0558	0,88	0,57	1,35	0,5489	0,49	0,24	0,98	0,0439	0,46	0,13	1,57
Singleton	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1
<500G	74,7	22,8	245	<.0001	42,6	13,2	138	<.0001	79,3	17,2	365	<.0001	.	.	.
500-749G	16,1	10,5	24,7	<.0001	14,7	9,12	23,9	<.0001	8,05	3,88	16,7	<.0001	16,1	6,03	43,2
750-999G	3,13	2,2	4,46	<.0001	3,11	2	4,83	<.0001	3,2	1,76	5,81	0,0001	2,25	0,8	6,29
1000G+	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1
Iugr +	0,37	0,24	0,58	<.0001	0,39	0,23	0,65	0,0004	0,48	0,23	1,01	0,0537	0,41	0,14	1,19
Iugr -	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1
Inborn	0,68	0,42	1,08	0,1015	0,59	0,34	1,02	0,0583	0,75	0,34	1,67	0,4837	1,44	0,31	6,63
AT/IUT	0,73	0,47	1,15	0,1769	0,65	0,38	1,09	0,1039	0,75	0,35	1,63	0,468	1,58	0,36	7,01
Outborn	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1
> 2	1,24	0,63	2,43	0,5286	1,8	0,88	3,68	0,1094	0,83	0,23	2,95	0,7702	.	.	.
Twin	0,64	0,44	0,93	0,0181	0,83	0,54	1,27	0,3846	0,45	0,22	0,92	0,0281	0,52	0,18	1,51
Singleton	1	1	1	.	1	1	1	.	1	1	1	.	1	1	1

OR: odds ratio; LB and UB: respectively Under and Upper Bound of its 95% confidence interval; P: P-value testing OR=1

Overall mortality and early neonatal mortality were negatively influenced by GA, BW, and absence of IUGR. We were not able to demonstrate an independent significant effect of origin on outcome, excepted in the birth weight analysis of early neonatal mortality. In a model also including NICU this variable significantly ($p < 0.0001$) related with overall mortality and borderline significant ($p = 0.08$) with early neonatal mortality (Fig. 9.).



Morbidity

There were 1596 survivors at discharge, of which 339 (21,2%) developed CLD, 48 (3%) ICH>3 and 42 (2,6%) cystic periventricular leucomalacia at 36 weeks PMA.

IUGR was noted in 338 (21,2%), ICH<3 in 274 (17,2%), NEC/IP in 125 (7,8%), Perinatal infection in 361 (22,6%) and Nosocomial infection in 486 (30,5%) neonates.

As there exists much co-linearity between many of the independent outcome variables therefore mainly GA category , BW category, origin, NIC, gender, multiple pregnancy were entered in the logistic regression models.

Although more outborns needed resuscitation than inborns or than IUTR, origin became less important when NICU was included in the regression model (data not shown).
Potential variables which on the basis of the literature could influence the development of CLD were introduced. The variables, GA category, IUGR, RDS, surfactant, airleak, nosocomial infection, NEC/IP were not retained by the model. However CLD at 36 weeks postmenstrual age was mostly determined by Inborn status, boy-gender, more than 7 days on the ventilator or more than 7 days on CPAP, and more aggressive treatment of PDA(data not shown) (table 9).

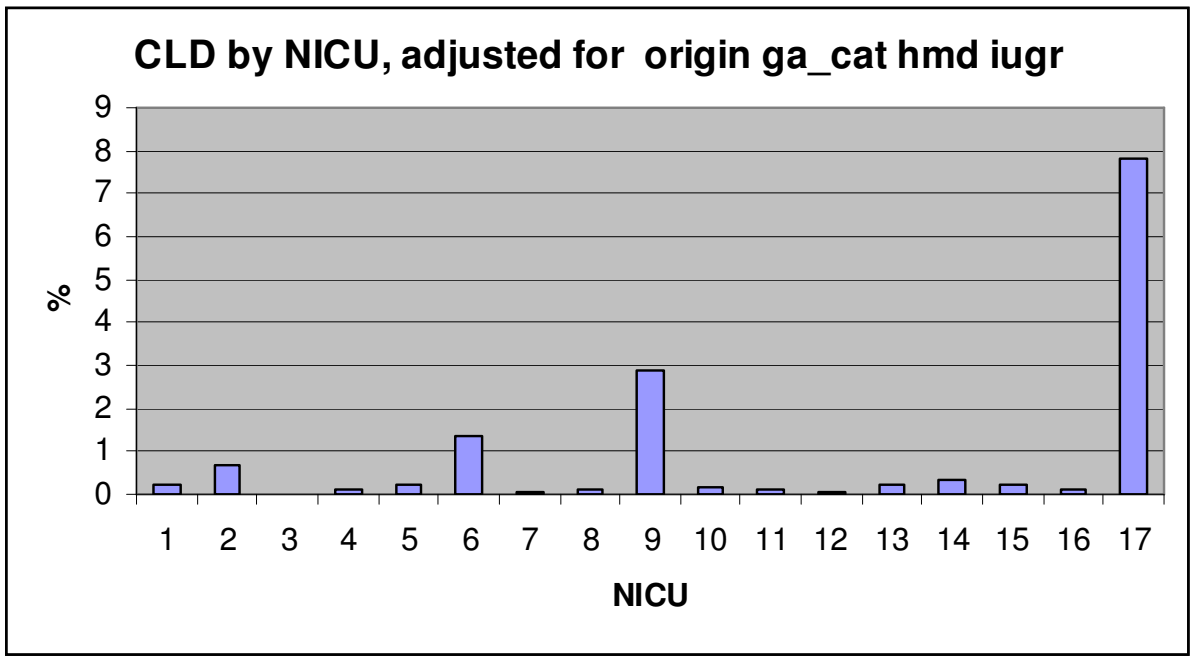
Table 9. : determinants of CLD_36w, including PDA, for all GA categories

		OR°	*LB°*	*UB°*	*P°*
Origin	Inborn	1.91	1.20	3.04	0.0067
Origin	AT/IUT	1.24	0.78	1.97	0.3624
Origin	Outborn	1.00	1.00	1.00	.
RDS	Yes	1.42	0.96	2.12	0.0816
RDS	No	1.00	1.00	1.00	.
IPPV_D	<25 h	1.35	0.73	2.49	0.3378
IPPV_D	< 24 h –7days	0.89	0.60	1.32	0.5558
IPPV_D	8 days –28 days	4.00	2.65	6.04	<.0001
IPPV_D	> 28 days	9.54	5.10	17.8	<.0001
IPPV_D	No	1.00	1.00	1.00	.
nCPAP_D	<25 h	0.96	0.53	1.74	0.8885
nCPAP_D	< 24 h –7days	1.37	0.87	2.17	0.1796
nCPAP_D	8 days –28 days	2.09	1.36	3.24	0.0009
nCPAP_D	> 28 days	3.73	2.35	5.94	<.0001
nCPAP_D	No	1.00	1.00	1.00	.
gender	Boys	1.37	1.04	1.81	0.0268
gender	Girls	1.00	1.00	1.00	.

OR: odds ratio; LB and UB: respectively Under and Upper Bound of its 95% confidence interval; P: P-value testing OR=1

If categories of days on ventilation or categories of days on CPAP were omitted there still existed an independent influence by IB status and RDS but also by GA category. GA category seemed to show a stronger influence on CLD followed by RDS and then IB status (data not shown) (data not shown). Introducing NICU in the model also showed an independent influence on CLD at 36 weeks postmenstrual age (Fig 10).
When chronic lung disease was adjusted for origin, GA category, RDS and IUGR, NICU still showed an independent influence on CLD at 36 weeks post menstrual age.

Fig.10. CLD at 36 weeks postmenstrual age corrected for origin, GA category, RDS and IUGR



For neonates with GA<29 weeks no difference in rate of CLD at 36 weeks for type of origin could be demonstrated, however CLD was associated with lower BW categories (data not shown) and lower GA categories, boy-gender and RDS. Respiratory treatment did not influence CLD at 36 weeks PMA as no differences were found for days on IPPV and for days on CPAP between Inborns and IUTR, and as more outborns were ventilated than inborns (table 10). However inborns had more days on CPAP than outborns (data not shown).

Table 10. CLD versus Origin, adjusted for GA and HMD, in neonates having a GA < 29 weeks

	OR°	*LB°*	*UB°*	*P°*
GA 23-24 w	2,93	1,02	8,41	0,0456
GA 25 w	3,39	1,8	6,35	0,0001
GA 26 w	2,07	1,25	3,44	0,0050
GA 27 w	1,83	1,17	2,86	0,0082
GA 28 w	1	1	1	.
Inborn	1,17	0,63	2,15	0,6240
AT/IUT	0,95	0,53	1,73	0,8768
Outborn	1	1	1	.
HMD +	2,45	1,40	4,29	0,0018
HMD -	1	1	1	.

OR: odds ratio; LB and UB: respectively Under and Upper Bound of its 95% confidence interval; P: P-value testing OR=1

In a next model containing potential variables which on the basis of the literature could influence the development of CLD for neonates less than 29 weeks, the variables, GA category, origin, gender, RDS, surfactant, airleak, nosocomial infection, NEC/IP were not retained by the model. On the other hand CLD at 36 weeks postmenstrual age was mostly determined by the presence of IUGR, more than 7 days on the ventilator or more than 7 days on CPAP, and more aggressive treatment of PDA (table 11).

Table 11.The influence of potential variables on CLD at 36 weeks in neonates with a GA < 29 weeks

	Sig.	Odd ratio	95,0% C.I.	
			Lower	Upper
Cat_GA <25wks		1	1	1
Cat_GA 25wks	,513	1,443	,480	4,335
Cat_GA 26 wks	,328	1,705	,585	4,971
Cat_GA 27 wks	,116	2,318	,813	6,605
Cat_GA 28 wks	,384	1,597	,557	4,575
gender boy	,044	1,487	1,012	2,187
HMD	,945	,976	,496	1,923
surfactant	,313	,774	,470	1,274
Airleak YES		1	1	1
airleak pneumothorax	,533	,805	,407	1,592
airleak other	,396	,690	,293	1,625

Nosinf	,910	,977	,649	1,471
NECIP	,168	,666	,375	1,186
IPPVd NO		1	1	1
IPPVd <25 hrs	,189	1,850	,738	4,634
IPPVd 25hrs-7d	,694	1,144	,586	2,234
IPPVd 8d-28d	,000	3,952	1,964	7,952
IPPVd >28d	,000	9,559	3,919	23,318
nCPAPd NO		1	1	1
nCPAPd <25hrs	,005	4,439	1,567	12,578
nCPAPd 25hrs-7d	,000	6,681	3,057	14,603
nCPAPd 8d-28d	,000	6,061	3,045	12,066
nCPAPd >28d	,000	13,778	6,904	27,496
Iugr	,067	1,735	,961	3,131
tPDA NO		1	1	1
tPDA medical	,002	1,953	1,274	2,994
tPDA surgical	,021	2,096	1,120	3,924
inborn		1	1	1
IUTR	,838	,958	,638	1,439
outborn	,907	,962	,503	1,840

Categorized number of days of artificial ventilation (IPPV_D): (1) = ≤ 24 hrs; (2) = > 24 hrs - 7 days; 3 = 8 days - 28 days; (4) = > 28 days;

Categorized number of days of nasal CPAP (nCPAP_D): (1) = ≤ 24 hrs; (2) = > 24 hrs - 7 days; (3)= 8 days - 28 days; (4) = > 28 days;

Treated Patent Ductus Arteriosus (tPDA): (1) = fluid restriction/diuretics and/or NSAID's; (2) = surgery

NICU also independently influenced CLD at 36 weeks PMA (data not shown)

However for neonates with GA>28 weeks CLD at 36 weeks was determined by outborn status, boy-gender, treated PDA, more than 7 days on CPAP and by NICU (latter data not shown).

In a next model potential variables which could have an influence on the development of CLD at 36 weeks PMA for neonates with a birth weight less than 1001 gram were introduced. The variables, origin, gender, GA categories, RDS, surfactant, airleak, treated PDA, nosocomial infection, NEC/IP

were not retained in the model. Therefore CLD at 36 weeks PMA was mostly determined by more than 7 days on the ventilator or more than 7 days on CPAP. NICU also influenced CLD at 36 weeks PMA.

For neonates > 1000 g CLD36 was influenced by inborn status, origin, male gender, treated PDA, partially by more than 7 days on the ventilator or more than 7 days on CPAP. And also by NICU (data not shown)

Need of extra oxygen at 28 days in survivors

Multivariate logistic regression analyses showed the influence of origin (IUTR) , GA category and BW category, surfactant and IUGR (table 12).

Table 12. Determinants for extra oxygen at 28 days in survivors.

Determinant	***OR°***	***LB°***	***UB°***	***P°***
Inborn	1,63	0,97	2,76	0,0676
IUT	2,14	1,29	3,56	0,0034
Outborn	1	1	1	.
23-24 w	15,5	3,76	64,1	0,0002
25 w	21,6	9,34	49,9	<.0001
26 w	8,25	4,83	14,1	<.0001
27 w	6,36	4,07	9,93	<.0001
28 w	3,45	2,3	5,19	<.0001
28 w +	1	1	1	.
Surfactant +	4	2,91	5,49	<.0001
Surfactant -	1	1	1	.
Mult. > 2	1,28	0,57	2,9	0,551
Twin	1,01	0,71	1,43	0,962
Singleton	1	1	1	.
Iugr +	1,16	0,75	1,8	0,4938
Iugr -	1	1	1	.

.

Inborn	1,32	0,85	2,05	0,2189
IUT	1,69	1,1	2,6	0,0164
Outborn	1	1	1	.
<500G	1,00E+11	0	.	0,9993
500-749G	16,1	9,1	28,6	<.0001
750-999G	4,88	3,63	6,57	<.0001
1000G+	1	1	1	.
Surfactant +	4,04	3,08	5,29	<.0001
Surfactant -	1	1	1	.
Mult. > 2	1,15	0,58	2,31	0,6842

Twin	0,99	0,73	1,33	0,9317
Singleton	1	1	1	.
Iugr +	0,29	0,19	0,47	<.0001
Iugr -	1	1	1	.

For the 48 survivors with a **large ICH >**3 the gestational age category <28 weeks was a determining factor, whereas only inborn status showed a non-significant trend not to develop large ICH (table13).

Table 13. : determinants of ICH ≥ 3 in 48 survivors

Determinant	OR°	LB°	UB°	P°
Inborn	0.48	0.22	1.07	0.0711
IUT	0.64	0.31	1.34	0.2386
Outborn	1.00	1.00	1.00	.
GA < 25 w	6.78	1.53	30.0	0.0117
GA 25 w	5.18	1.93	13.9	0.0011
GA 26 w	3.27	1.33	8.05	0.0101
GA 27 w	2.73	1.22	6.14	0.0148
GA 28 w	1.82	0.82	4.07	0.1430
GA > 28 w	1.00	1.00	1.00	.

OR: odds ratio; LB and UB: respectively Under and Upper Bound of its 95% confidence interval;
P: P-value testing OR=1

When NIC, RDS, gender and IUGR were introduced in the model only RDS had an independent influence on severe IVH. However Inborn status showed less severe IVH, and GA category <25 weeks more severe IVH. IVH grades 1 and 2 were independently influenced by all gestational age categories, and marginally by IUTR status. NICU, except for one unit did not have any influence (data not shown).

Cystistic periventricular leukomalacia (cPVL) noted in the 42 survivors

Cystic PVL was not influenced by origin, although there was a trend for IUTR, nor, nor by perinatal infection or nosocomial infection. However it was best explained by a model including GA categories less than 27 weeks, and IUGR, and NIC (NIC data not shown) (table 14).

Table 14. Determinants of Cystistic periventricular leukomalacia for 42 survivors

Determinant	*OR°*	*LB°*	*UB°*	*P°*	*Determinant*	*OR°*	*LB°*	*UB°*	*P°*
Inborn	0,66	0,28	1,52	0,3257	Inborn	0,58	0,21	1,6	0,2905
/IUT	0,43	0,18	1,02	0,0554	IUT	0,45	0,16	1,27	0,1314
Outborn	1	1	1.		Outborn	1	1	1.	
Boys	0,86	0,46	1,63	0,6499	Boys	0,8	0,37	1,75	0,5781

23-24 wks	17,90	4,36	73,6	<.0001	23-24 w				
25 wks	6,00	1,88	19,1	0,0025	25 w	15,8	2,08	120	0,0076
26 wks	3,40	1,20	9,62	0,0211	26 w	4,02	0,84	19,3	0,0817
27 wks	1,76	0,57	5,42	0,3266	27 w	2,67	0,67	10,6	0,1626
28 wks	2,20	0,88	5,49	0,0915	28 w	1,75	0,45	6,85	0,4212
>28 wks	1	1	1	.	>28 w +	2,14	0,71	6,41	0,1763
Iugr +	3,15	1,55	6,39	0,0015	Iugr +	3,19	1,36	7,48	0,0075
Pn_inf +	1,45	0,72	2,91	0,2962	Nos Inf +	1,57	0,68	3,6	0,2872

OR: odds ratio; LB and UB: respectively Under and Upper Bound of its 95% confidence interval; P: P-value testing OR=1
Pn: perinatal infection; Nos: nosocomial infection

The combination of CPVL and/or IVH in 84 survivors was not influenced by origin but was best explained by a model including lower GA-cat , IUGR and NIC.(data not shown) and to a lesser extend by inborn status (Table 15).

Table 15. :Determinants of both CPLV and ICH in 84 survivors

Determinant	***OR°***	***LB°***	***UB°***	***P°***
Inborn	0.57	0.29	1.10	0.0951
AT/IUT	0.59	0.31	1.12	0.1041
Outborn	1.00	1.00	1.00	.
Boys	0.94	0.59	1.52	0.8111
Girls	1.00	1.00	1.00	.
23-24 w	10.6	2.96	37.8	0.0003
25 w	6.31	2.68	14.9	<.0001
26 w	3.71	1.73	7.95	0.0007
27 w	2.09	0.96	4.57	0.0644
28 w	2.00	1.00	3.98	0.0495
28 w +	1.00	1.00	1.00	.
Iugr +	1.79	1.00	3.20	0.0483
Iugr -	1.00	1.00	1.00	.

OR: odds ratio; LB and UB: respectively Under and Upper Bound of its 95% confidence interval; P: P-value testing OR=1

ROP is problematic since too many neonates were not tested (table 16)

Table 16.

parameter	level1	oddsrat	lower95	upper95	probchisq
gacat	1	2,29	1,82	2,87	<.0001
gacat	2	0,66	0,5	0,86	0,0025
sex	1	1,8	0,95	3,4	0,0696
sex	2	0,87	0,61	1,25	0,4573

origin1	1	1,12	0,68	1,84	0,6588
origin1	2	0,46	0,35	0,61	<.0001
origin2	1	0,97	0,61	1,54	0,882
origin2	2	0,99	0,78	1,26	0,933
o2	1	1,86	1,27	2,72	0,0015
o2	2	0,47	0,32	0,7	0,0002

Level1=1: OR of a ROP >2 vs ROP < 3
Level1=2: OR of a RPO not tested vs ROP < 3
Gacat = 7 – (ga_cat*1) => base is > 28 weeks;

The results of a multivariable, polychotomous logistic regression mainly showed a significant and strongly negative association of ROP GE 3 and gestational age category (OR:2,29 (95%CI: 1,82;2,87) per descending GA cat (base 29 weeks or more)], a significant and strongly positive association with O2therapy (OR:1,86 (95%CI: 1,27;2,72)] and a borderline positive association with male sex (OR:1,80 (95%CI: 0,95;3,40)]. No significant association between ROP and origin could be established. However a significant and strongly positive association of ROP untested and gestational age category (OR:0,66 (95%CI: 0,50;0,86) per descending GA cat (base 29 weeks or more)], a significant and strongly negative association of ROP untested and oxygen therapy (OR:0,47 (95%CI: 0,32;0,70)] and no significant association with gender ((OR:0,87 (95%CI: 0,61;1,25)). Compared with outborns inborns were less often associated with ROP untested (OR:0,46 (95%CI: 0,35; 0,61)), whereas we could establish such association when comparing IUT/AT with outborns ((OR:0,99 (95%CI: 0,78; 1,26)).

PN_infection (one NIC omitted) was not influenced by origin, nor by BW category or multiple pregnancy, but by GA category, ET (endotracheal intubation and cardiac compression combined), borderline by IUGR, and also by NIC (detailed data not shown) (Table 17)

Table 17. Determinants of perinatal infection in 16 NICU's (one unit omitted)

		Sig.	Exp(B)	95,0% C.I.for EXP(B)	
				Lower	Upper
Step 1(a)	Cat_GA	,006			
	23-24 w	,724	,846	,333	2,145
	25 w	,752	,899	,466	1,735
	26 w	,081	1,550	,947	2,537
	27 w	,000	2,129	1,404	3,228
	28 w	,088	1,422	,949	2,132
	iugr(1)	,058	1,482	,987	2,225

	gen(1)	,250	1,181	,890	1,567
	orig	,809			
	orig(1)	,821	,947	,593	1,514
	orig(2)	,556	,880	,575	1,346
	NIC	,000			
	mulpreg	,509			
	mulpreg(1)	,746	1,152	,488	2,719
	mulpreg(2)	,912	,951	,391	2,315
	ETrea	,000			
	ETrea(1)	,016	,188	,049	,729
	ETrea(2)	,167	,381	,097	1,499

a Variable(s) entered on step 1: Cat_GA, iugr, gen, orig, NIC, mulpreg, ETrea.

Nosocom_infect without unit 4 was not influenced by origin but by **GA category, BW category** and NIC (model with BW category not shown but very significant p<0.00) (Table 18).

Table 18. : Determinants of nosocomial infection in 16 NICU's (one NICU excluded)

Determinant	***OR°***	***LB°***	***UB°***	***P°***
23-24 w	1.61	0.77	3.37	0.2068
25 w	2.85	1.75	4.64	<.0001
26 w	3.00	2.00	4.50	<.0001
27 w	3.02	2.12	4.32	<.0001
28 w	2.52	1.82	3.51	<.0001
28 w +	1.00	1.00	1.00	.
Inborn	1.36	0.93	1.99	0.1123
AT/IUT	1.24	0.86	1.80	0.2500
Outborn	1.00	1.00	1.00	.
Iugr +	1.12	0.83	1.51	0.4635
Iugr -	1.00	1.00	1.00	.
Boys	1.37	1.08	1.73	0.0085
Girls	1.00	1.00	1.00	.
ET Int +	1.04	0.79	1.36	0.8007
ET Int -	1.00	1.00	1.00	.
Mult. > 2	1.15	0.64	2.06	0.6485
Twin	0.94	0.72	1.22	0.6275
Singleton	1.00	1.00	1.00	.

OR: odds ratio; LB and UB: respectively Under and Upper Bound of its 95% confidence interval; P: P-value testing OR=1

Length of stay:

By linear regression LOS seemed to be independently influenced by type of origin and type of NIC (data not shown for origin and NIC), GA-Cat, BW_Cat, respiratory outcome (in terms of CLD at 36

weeks PMA, oxygen dependency at 28 days or length of ventilation or CPAP), nosocomial infection, NEC or IP, thoracic or abdominal surgery (Table 19).

Table 19: Determinants length of stay

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95% Confidence Interval for B		Correlations			Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	16,612	3,364		4,938	,000	10,014	23,209					
	Cat_GA	1,636	,556	,061	2,943	,003	,546	2,726	-,148	,069	,052	,724	1,381
	NEC/IP	8,713	2,841	,062	3,067	,002	3,141	14,285	,185	,072	,054	,757	1,322
	CLD36w	17,574	1,929	,183	9,109	,000	13,790	21,358	,416	,208	,160	,762	1,312
	tPDA	-1,265	1,657	-,018	-,763	,445	-4,515	1,985	,320	-,018	-,013	,541	1,850
	ICH=3	-11,738	2,705	-,082	-4,340	,000	-17,043	-6,433	-,122	-,101	-,076	,868	1,152
	nosinf	8,221	1,656	,099	4,964	,000	4,973	11,470	,342	,115	,087	,781	1,281
	IPPVd	2,833	,689	,096	4,110	,000	1,481	4,185	,358	,096	,072	,562	1,780
	O2>28d	15,859	2,017	,176	7,862	,000	11,903	19,815	,475	,181	,138	,614	1,628
	nCPAPd	8,025	,539	,312	14,900	,000	6,969	9,081	,517	,329	,262	,703	1,423
	Thorsur	17,097	4,089	,089	4,182	,000	9,078	25,116	,240	,097	,073	,674	1,484
	Abdsur	11,964	3,062	,081	3,907	,000	5,958	17,970	,247	,091	,069	,720	1,388
	iugr	1,999	1,689	,022	1,183	,237	-1,314	5,311	-,074	,028	,021	,924	1,082
	cPVL	-,770	4,059	-,003	-,190	,850	-8,731	7,191	,067	-,004	-,003	,956	1,046
	conmal	-1,890	1,325	-,026	-1,426	,154	-4,489	,709	-,025	-,033	-,025	,957	1,045

a. Dependent Variable: stay

Discussion/Conclusion

Except for more inborns developing chronic lung disease at a post menstrual age of 36 weeks, the present analysis did not show a meaningful significant difference between inborns in utero transfers and outborns with a birth weight less than 1500 gram for the major outcomes, mortality, IVH (grade 3-4), PVL, NEC/PERF, and ROP. However many of the outcome variables such as early neonatal mortality, chronic lung disease at 36 weeks, cystic periventricular leukomalacia, perinatal and nosocomial infection, length of stay were influenced by the anonymous variable "NICU", meaning that specific neonatal unit characteristics may have influenced mortality and morbidity.

A major limitation for the present data-set and analysis is the non-availability of maternal pregnancy complications, the antenatal administration of corticoids, duration of rupture of the membranes, placental abnormalities, mode of delivery, fetal distress.

Based on the NICaudit data base 85.6% of the neonates < 1500gram admitted to an NICU in Belgium in 2004 and 2005 combined (n=1845) were born in a maternity unit with a NICU on site and 14,4 % (n=265) were born in a hospital without an NICU and were transferred to a NICU. Of the total admission rate 39.6% were inborns and 46.1 % concerned IUTR.

Although in some countries [17], still many neonates with a birth weight less than 1500 gram are born in maternity units without a level III neonatal unit, and therefore are becoming more de-regionalized, it seems that in Belgium 85,6% of the neonates <1500gram can be assumed to be born in a maternity unit with a level III neonatal unit. In the 1999 Europet study an inborn rate, including IUTR, of 77.4% was reported and in 2008 the MOSAIC project reported 82%, both for neonates with a gestational age less than 32 weeks [16] [29].

Whether the 14% (n=265) postnatal transfers, 64% with a gestational age >28 weeks or 36% less than 29 weeks, could have been preventable extra-uterine transfers can presently not be clarified: data, e.g. on rupture of the uterus, placental abruption, vaginal bleeding, risk for delivery during transport, which are all contraindications for maternal transfer with the fetus in utero, were not available [11].

The total group of VLBW neonates was heterogeneously spread out over the 17 participating NICU's (data not shown) and thus may be responsible for divergent outcomes in terms of type of origin.

Gesational age and birth weight were lower for IUTR than for inborns and less than for outborns. Combining inborns and IUTR, there was no difference in GA across type of origin. It could be that

maternal pathologies or fetal distress were more severe in IUTR's needing delivery at a lower gestational than for inborns. Apgar scores at 5 minutes of life did however not differ between inborns and IUTR. The total group of outborns and also those with a GA less than 29 weeks had lower Apgar scores at 5 minutes, and consequently needed more resuscitation at birth, expressed as endotracheal intubation and cardiac compressions and needed more days on the ventilator in the NICU. This could reflect more distress at or before birth for several reasons, such as fetal distress, placental abruption, rupture of the uterus, difficult delivery process (extraction). Also it seems reasonable to accept that outborns are transferred when they still have a chance of survival and therefore, but probably a not neglectable number of these neonates may have been intubated before transport, but registered as having been resuscitated, to insure a safe and stable transfer to a neonatal intensive care unit.

More IUGR but fewer males were seen in IB versus IUTR or OB. However for males no difference was noted for those neonates with a GA les than 29 weeks. No specific maternal or fetal data were collected in the NICaudit database which could have affected in utero growth (placental insufficiency, oligo-hydramnion, hypertensive disease) which may have explained some of the IUGR rate differences between the types of origin. Neither do we know whether more males had died in the delivery room or that proportionally more female neonates survived in the regional hospital and were transferred to a NICU. No differences across type of origin were noted for multiplets or congenital anomalies. Neonates resulting from a multiple pregnancy covered a large percentage, i.e. 32%, of the total admissions of neonates with a birth weight less than 1500 gram. Certainly artificial reproduction techniques may very well be at the base of this phenomenon. Between 32 and 57% of neonates resulting from spontaneous and assisted reproductive therapy multifetal pregnancies are reported to be admitted to a NICU of which 30% have a gestational age less than 32 weeks.[44].

Only 20 of 136 neonates with a severe congenital anomaly, chromosomal or severe possibly lethal anomaly, were outborns. It cannot be excluded that some severely abnormal neonates died in the regional hospital as treatment may have been considered futile.

Overall mortality at discharge was not different between inborn, IUTR or outborn neonates, but a wide range was noted between NICU's (5.6-23,2 %). Although less inborns died in the early neonatal period than IUTR or outborns, this was not significant. Early and late neonatal mortality were independently influenced by GA, BW, and IUGR. NICU also influenced early neonatal mortality. The latter needs to

be placed in the context of ethical decision making and local guidelines which understandably may vary between NICU's and countries[15;54;73].

In the Mosaic project the mortality rate before discharge for neonates born in 2003 at less than 32 weeks gestational age in Flanders was 16% which was comparable to other Mosaic regions in Europe, i.e. 14% (range 7-22%) where it is 13.4% in the present report covering 2004-2005. [29].On the other hand it is clear that VLBWI born and cared for in hospitals without a level III unit show a higher mortality than those born in a hospital with a level III unit [52].

Proportionally more inborns developed chronic lung disease at 36 weeks PMA than IUTR or outborns. Less inborns were ventilated than IUTR and less IUTR than outborns, but more inborns were treated with CPAP than IUTR and outborns. On the other hand less inborns needed oxygen at 28 days of life than IUTR and less outborns needed oxygen at 28 days than IUTR. When the group inborn and IUTR was combined this group showed significantly more CLD at 36 weeks PMA than the outborn group, while the number of neonates with a GA less than 29 weeks with CLD at 36 weeks PMA or in need for oxygen longer than 28 days was similar for the inborn, IUTR and outborn group. Anonymous NIC showed an independent effect on CLD at 36 weeks PMA in survivors with a range of 1.2 to 79.9% between NICU's. In the present study the overall rate was 21.2%% in survivors. In the MOSAIC project the rate was 15.5% (14.5% for Flanders) with a range of 9.7 to 25.6% between the 10 European regions. Others also reported a wide variability between centres. [32], 12% in a population <33 weeks [65], a rate of 17% (4-26%) in VLBW infants by [20]. Therefore some of these findings can probably be explained by the unit characteristics[67] [37]. First, one must consider that very different definitions have been used throughout the passed years and most units, also in Belgium, still have not fully adopted the new proposals for a uniform definition of chronic lung disease at a PMA of 36 weeks [31]. Second, no uniform protocols were applied across units for, e.g. respiratory support, treatment of PDA or the use of oxygen saturation limits. This is further supported by the wide range of CLD at 36 weeks PMA (from less than 5% to 70%) and also a wide range of need for oxygen at 28 days of life between NICU's. This is supported by the literature showing that among 20 centers registered in the Vermont Oxford database CLD at 36 PMA ranged from 13.4 to 66.7 % in 2001. However applying a number of quality improving measures (use of surfactant in the delivery room, reducing the time to first surfactant and the use of conventional ventilation) this range dropped to a range of 4.0% to 58.3% in 2003 [49] [27;59].Third, it cannot be excluded that mothers of inborn and IUTR neonates had a higher disease severity when they were admitted to the obstetrical ward (data were not collected), also we do not have data on antenatal

corticoid use, which is important in the prevention of RDS and thus also the development of chronic lung disease. Fourth, we cannot exclude a coding error or firm adherence to the coding definition for CLD at 36 PMA in the database, and therefore this needs further exploration. And finally, recently genetics has been implicated in the development of chronic lung disease, however this factor only may not explain the heterogeneous spread of CLD over the different units. Therefore an epiphenomenon such as the unit characteristics needs further exploration [35].

The rate for severe IVH was 7.5% which is similar to the recently reported 12% by [20] and the MOSAIC project [80]. Although not significant, less inborns developed severe intraventricular hemorrhage than IUTR and outborns. Significantly less inborns and IUTR neonates with a GA less than 29 weeks developed severe IVH. This is in accordance with the literature. A higher incidence of IVH (23%) has been reported in the 1990ies for outborns [68] [12;64]2001, [75], [45]. This underscores the presently held view that VLBWI have a better outcome when they are born in a tertiary neonatal unit [13;46;75] [22;52;53;60].
Although the recent literature reports that severe IVH is influenced by NICU , this was not the case in the present study [67], nor when all neonates (N=138) were analysed nor for the survivors with severe IVH.
Cystic periventricular leucomalacia occurred in 2.9% of the survivors and was influenced by GA category, IUGR, perinatal infection and NIC, but not by origin. The combined outcome IVH>3 and /or cPVL was influenced by GA category =<25 weeks, inborn status, IUGR and perinatal infection but not by NIC nor by nosocomial infection.. However this combined outcome related only to 17 survivors. As the diagnosis of (cystic), periventricular leukomalacia is usually made by brain ultrasound.

In relation to origin no significant differences were noted for RDS, perinatal infection, nosocomial infection, necrotising enterocolitis or isolated perforation, treated patent ductus arteriosus. However all of these morbidities were influenced by the variable NICU, besides gestational age - or birth weight category. This again shows, as stated above for other morbidities, the likely influence of unknown perinatal factors or specific unit characteristics.
Retinopathy of prematurity with a grade equal or more than III occurred in 3,1 percent of the survivors and seemed to occur less in outborns. However 21% of them were not tested before discharge.

Therefore no meaningful conclusions can be made other than that ophthalmologic follow up after discharge needs to be registered to make sure that development of ROP is not missed.
As could be expected LOS was independently influenced by many variables (table 20), including origin and NIC. Some of these factors can be manipulated and are dependent on local policies, such as: timely back transfer to a regional hospital or to the local non-intensive care unit, adherence to strict hygienic measures to reduce nosocomial infections, [33].

In conclusion, the majority (86 %) of the 1845 neonates with VLBW (<1500 gram) admitted to 17 of the 19 NICU's in Belgium over the years 2004- and 2005, were born in a maternity unit with a NICU on site and only 14 % (n=265) were born in a hospital without a NICU and were transferred to a NICU. Although only 14.4% of the admitted VLBW neonates were outborns it remains to be determined whether some of these extra-uterine transfers could have been prevented. No major differences between inborns, intra-uterine transfers and outborns with a birth weight less than 1500 gram for the major outcomes, mortality, IVH (grade 3-4), PVL, NEC/PERF, CLD36 and ROP were noted. For CLD at 36 weeks PMA inborn status was an independent, but yet unexplained, risk factor. Fewer neonates with a gestational less than 29 weeks showed severe IVH when they were born in the hospital with a NICU. Perinatal data were not systematically registered and thus may be a major limitation in explaining some of the results. Likewise "NICU" had a major influence on many of the main outcome variables, but its specific characteristics were not available. The total group of VLBW neonates was heterogeneously spread out over the 17 participating NICU's and thus may be responsible for divergent outcomes in terms of type of origin. Finally, the contribution of genetic factors to a number of neonatal pathologies may not be neglected as recently demonstrated [19;34]

Recommendations:
- Although 85% of the VLBWI were born in a hospital with a tertiary unit on-site and IUTR is to be recommended, more direct bookings in tertiary perinatal units of neonates with an expected birth weight less than 1500 gram or with an expected gestational age less than 32 weeks may further improve total outcome of these neonates. Considering the facilities offered in Belgian perinatal centres and those hospitals not designated as perinatal centres it should be recommended to deliver and admit more than

90% of the low birth weight infants < 1500 grams or less than 32 weeks in a perinatal center and virtually 100% for those less than <1000gram birth weight or a gestational age less than 28 weeks.
- As few outcome variables were influenced by inborn-, in utero- or outborn status but rather more by the effect of NICU related factors, in debt analysis of the unit characteristics should be performed (among them heterogeneity of the type of neonates, performance data, diagnostic and treatment protocols, techniques, infection control) [71]. Elucidation of these factors may lead to collaborative initiatives between the Belgian NICU's to further improve outcome not only for very low birth weight and very preterm infants items but likely also for all sick neonates admitted to a NICU. This type of improvement initiatives may eventually also lead to cost reduction[26;50;51] [56].
- Future analyses should include important perinatal factors which now were missing and certainly may have influenced some of the major outcomes.
- Attention should be payed to improve correct data acquisition (diagnostic coding and adherence to coding criteria)

Appendix

explanation and coding of variables available in the NICaudit database and indicated by * for those used in the present analysis

a. categorical

- NICN: Anonymous service identifier
- *gender
- *origin:
    - Inborn (IB): all neonates originating from mothers booked to deliver in a MIC.
    - Antenatal transfer (ANTR): a not medically supervised maternal transfer for a maternal or fetal condition needing care at a tertiary perinatal center (congenital anomaly, allo-immunisation, high order multiple pregnancy.)
    - In utero transfer (IUTR): an inter-hospital transfer with medical supervision for a maternal or fetal condition needing immediate tertiary perinatal care or delivery.

    - Outborn (OB): all neonates transported from a N* to a NICU, including home births and other referrals (ambulance, taxi..)
    - Home birth (N=5): these were included in the outborn group.
- *GA was categorized as:
    - 1: GA <25 weeks
    - 2: GA = 25 weeks
    - 3: GA = 26 weeks
    - 4: GA = 27 weeks
    - 5: GA = 28 weeks
    - 6: GA > 28 weeks
- *BW was categorized as:
    - 1: BW <500gram
    - 2: BW = or >500 and < 750 gram
    - 3: BW = or >750 and <1000 gram
    - 4: BW >1000 gram

- Conception : 0 = spontaneous; 1 = ART (artificial reproductive technology); 2 = no data
- *Resuscitation (ET_rea): 0 = no endotracheal intubation; 1 = ET intubation; 2 = no data
- *In utero growth retardation (IUGR), i.e. birth weight <10th percentile according to the 1996 SPE (ref) growth curves.
- *Multiple pregnancy (mult_preg): 0 = single; 1 = twin; 2 = high order multiplet (> 2)
- *Necrotising enterocolitis and /or intestinal perforation (NEC_IP) from NEC stage III and II according to Bell's criteria: 0 = no; 1 = yes
- *Hyaline membrane disease (HMD): 0 = no; 1 = yes:
- *Surfactant treatment (Surf): SF = surfactant: 0 = no; 1 = yes
- *Airleak: 0 = no; 1 = pneumothorax; 2 = other airleak(s)
- *Chronic lung disease at the postmenstrual age 36 weeks (CLD_36w): 0 = no ; 1 = yes; 2 = no data
- *Treated Patent Ductus Arteriosus (tPDA):: 0 = no; 1 = fluid restriction/diuretics and/or NSAID's; 2 = surgery
- *Intracranial haemorrhage ≥ grade 3 (ICHGE3)) according to Papile (ref) : 0 = no; 1 = yes

- *Cystic periventricular leukomalacia (cPVL): 0 = no; 1 = yes
- *Retinopathy of prematurity ≥ grade 3 (ROPGE3): (= inclusive dying infants): 0 = no; 1 = yes; 2 = not tested (= including non-survivors)
- Foetal infection (foet_inf), i.e. CMV, Toxoplasmosis: 0 = no; 1 = yes
- *Perinatal infection (< 72 hours) (pn_inf): 0 = no; 1 = yes
- *Nosocomial infection (≥ 72 hours) (nos_inf): 0 = no; 1 = yes
- *Congenital malformations (con_mal):: 0 = no; 1 = karyotype anomaly; 2 = non-chromosomal major congenital anomalies
- Categorized number of bloodtransfusions (bloodT): 0 = no; 1 = 1; 2 = 2 - 5; 3 = > 5; question mark = no data
- *Categorized number of days of artificial ventilation (IPPV_D): 0 = no; 1 = ≤ 24 hrs; 2 = > 24 hrs - 7 days; 3 = 8 days - 28 days; 4 = > 28 days; 5 = no data
- *Oxygen therapy longer than 28 days of life (O2GE28d): > 28 days: 0 = no; 1 = yes
- *Categorized number of days of nasal CPAP (nCPAP_D): 0 = no; 1 = ≤ 24 hrs; 2 = > 24 hrs - 7 days; 3 = 8 days - 28 days; 4 = > 28 days; 5 = no data
- Thoracic surgery (Thorsur): 0 = no; 1 = yes
- Abdominal surgery (Abdsur): 0 = no; 1 = yes
- Digestive sequelae (Digseq): 0 = no; 1 = stoma; 2 = (semi-)elementary formula or other
- *Destination (Destin):1 = home; 2 = internal transfer; 3 = external transfer; 4 = died
- *Death (died): 0 = no; 1 = yes
- Type of care before death (Caretyp):0 = not applicable; 1 = active care until death; 2 = withholding; 3 = withdrawal; 99 = unknown

b. Continuous variables:

- Age at admission (admday): in completed days (date of admission kind (DD-MM-JJ) – birth date (DD-MM-JJ)
- *Gestational age in weeks (GA)
- *Birth weight in grams (BW)
- *Apgar at 5 minutes (Ap_5)
- Weight at discharge (Diswght:)

- Length of stay in the NICU (LOS)

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