

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## Hospital Volume and Neonatal Mortality Among Very Low Birth Weight Infants

Dorothee B. Bartels, David Wypij, Paul Wenzlaff, Olaf Dammann and Christian F. Poets

*Pediatrics* 2006;117:2206-2214

DOI: 10.1542/peds.2005-1624

**This information is current as of June 24, 2006**

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/117/6/2206>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2006 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# Hospital Volume and Neonatal Mortality Among Very Low Birth Weight Infants

Dorothee B. Bartels, PhD, MSc<sup>a,c</sup>, David Wypij, PhD<sup>b</sup>, Paul Wenzlaff<sup>c</sup>, Olaf Dammann, MD<sup>d,e</sup>, Christian F. Poets, MD<sup>f</sup>

<sup>a</sup>Departments of Obstetrics, Pulmonology and Neonatology, and Epidemiology, Social Medicine and Health System Research, Hannover Medical School, Hannover, Germany; <sup>b</sup>Children's Hospital and Harvard School of Public Health, Boston, Massachusetts; <sup>c</sup>Center for Quality Assurance and Management in Health Care, Hannover, Germany; <sup>d</sup>Departments of Obstetrics and Pediatrics, Perinatal Infectious Disease Epidemiology Unit, Hannover Medical School, Hannover, Germany; <sup>e</sup>Neuroepidemiology Unit, Departments of Neurology, Children's Hospital and Harvard Medical School, Boston, Massachusetts; <sup>f</sup>Department of Neonatology, University of Tübingen, Tübingen, Germany

The authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

**BACKGROUND.** Very low birth weight infants (<1500 g) are at increased mortality risk. Data on the impact of NICU volume are sparse, in comparison with those on the level of care. We hypothesized that neonatal mortality would be higher in small NICUs (<36 very low birth weight admissions per year) than in large NICUs, with adjustment for volume of the delivery unit.

**METHODS.** We analyzed population-based data from a quality assurance program in Lower Saxony (Germany). Perinatal data for almost all very low birth weight infants born in 1991 to 1999 ( $n = 7745$ ) were available. Analyses were restricted to infants born at 24 to 30 weeks ( $n = 4379$ ). Data validation procedures, univariate data analyses, and logistic regression models based on general estimating equations were performed.

**RESULTS.** Neonatal mortality among infants admitted to NICUs was 12.2% in small NICUs and 10.2% in large NICUs. The mortality rate in small NICUs was increased significantly. Compared with infants from large delivery hospitals (>1000 births per year) and large NICUs, the adjusted odds ratio was 1.94 for neonates for whom both units were small, 1.75 for those from large delivery units but small neonatal units, and 1.16 for those for whom only the NICU was large. Stratification according to gestational age revealed the greatest impact on mortality for infants of <29 weeks.

**CONCLUSIONS.** Results suggest that creating larger perinatal centers may improve perinatal health care. The volume of the NICU was associated more strongly with 28-day mortality than was the volume of the delivery hospital, and it had the largest impact on survival for infants of <29 weeks.

[www.pediatrics.org/cgi/doi/10.1542/peds.2005-1624](http://www.pediatrics.org/cgi/doi/10.1542/peds.2005-1624)

doi:10.1542/peds.2005-1624

### Key Words

very low birth weight infant, neonatal mortality, hospital volume, regionalization

### Abbreviations

VLBW—very low birth weight  
SGA—small for gestational age  
OR—odds ratio  
CI—confidence interval

Accepted for publication Dec 21, 2005

Address correspondence to Dorothee B. Bartels, PhD, MSc, Departments of Obstetrics, Pulmonology and Neonatology, and Epidemiology, Social Medicine and Health System Research, Hannover Medical School, Carl-Neuberg-Strasse 1, OE 5410, 30625 Hannover, Germany. E-mail: bartels.dorothee@mh-hannover.de

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

**V**ERY LOW BIRTH weight (VLBW) infants (<1500 g) are at increased mortality risk.<sup>1-4</sup> The volume of the delivery unit and the size or level of the NICU seem to influence mortality.<sup>5-8</sup> Currently, there are no population-based studies of risk-adjusted VLBW mortality that control for both NICU volume and size of the delivery service.

Delivery hospitals and neonatal care units are often detached. This “decentralization” concept, with many small units, was reinforced (eg, in Germany) to minimize distance and duration of neonatal transport. Today, the obvious advantages of large perinatal centers and in utero transport, as well as economic benefits, have led to the quest for centralization. Unfortunately, supportive data are lacking.

In the absence of a specific classification system that quantifies the level of care, hospitals can be compared with respect to outcomes by using hospital caseload as a proxy. Most previous studies showed that high hospital volume was associated with better outcomes.<sup>9</sup> Difficulties in those studies included differences in case mixtures and study populations, varying definitions of hospital categories, presence of bias,<sup>10</sup> and focus only on specific procedures.<sup>11</sup>

Previous studies on neonatal outcomes and hospital volumes did not include both NICU volume and delivery hospital volume<sup>5-8</sup> and often did not, or did not sufficiently, include risk adjustments.<sup>7,12,13</sup> In particular, VLBW studies were often biased by the use of birth weight cohorts without gestational age limits.<sup>14,15</sup>

Each year, ~80 000 infants are born in the German state of Lower Saxony. Approximately 800 of these have birth weights of <1500 g. We hypothesized that VLBW neonates from high-volume NICUs ( $\geq 36$  VLBW admissions per year) would have a lower 28-day mortality risk, compared with neonates from low-volume NICUs, with adjustment for delivery hospital volume ( $\leq 1000$  or  $>1000$  deliveries per year). Moreover, we assumed a strong influence of gestational age. Our goal was also to offer population-based support for the design of NICU-level definitions and referral guidelines.

## METHODS

### Database

We used data from a well-established, ongoing, quality assurance program in the German state of Lower Saxony.<sup>16</sup> The obstetric database included perinatal data for 97% of all births. Neonatal data were available for all infants admitted to a NICU within 10 days after birth. The anonymous, originally separately recorded data of these 2 databases were linked by matching entries for specific variables, providing information about pregnancy, maternal risk factors, delivery, perinatal condition, treatment, and diagnosis at discharge. Because it is highly unlikely that a VLBW infant would be born at

home or not admitted to a NICU, we do not expect missing data.<sup>17</sup> Data were available for 7745 VLBW neonates, born between January 1, 1991, and December 31, 1999, in Lower Saxony. Eight of the 7745 infants were excluded because of improperly defined gestational age. Stillbirths ( $n = 868$ , 11.2%) were excluded from all additional analyses. Because we used a sample defined with an upper birth weight limit of 1500 g, we needed to introduce gestational age limits to minimize bias.<sup>14,15</sup> This resulted in 4604 infants with gestational ages of 24 to 30 weeks. Forty-six infants (1%) died during birth, 14 (1.1%) in small delivery hospitals and 32 (1%) in large delivery hospitals. Moreover, 141 (3.1%) died in the delivery hospitals, 51 (4%) in small units and 90 (2.7%) in larger units. As mentioned above, delivery hospitals and NICUs are mostly separate facilities in Germany. Because of this structure and contracts of some delivery hospitals with  $>1$  NICU, those infants could not be assigned to a specific NICU. Moreover, our main focus was on the effect of NICU volume, which is why those newborns were excluded. For 38 infants (0.8%), no additional data were available, either because of transfer to neighboring states or because of linkage failure for the perinatal and neonatal data. In total, data for 4379 infants were available for analyses. Study population characteristics are presented in Table 1.

The patient volume cutoffs between “small” and “large” used by the quality assurance program<sup>16</sup> for many years, and thus also used in this study, were  $\leq 1000$  versus  $>1000$  births per year for delivery hospitals and  $<36$  versus  $\geq 36$  VLBW admissions per year for NICUs. The small number of large hospitals in Lower Saxony justifies this relatively low cutoff value. Each newborn was assigned to the NICU where the child was mostly cared for during his or her first 4 weeks of life, because some (6.1%) were transferred shortly after birth to a different NICU, of potentially different size.

Among the 107 delivery units, 79 were small (27.2% of deliveries,  $n = 1190$ ) and 28 were large (72.8%,  $n = 3189$ ). Among the 36 NICUs, 26 to 29 were small (accounting for 37.7% of the neonates,  $n = 1652$ ) and 7 to 10 were large (accounting for 62.3% of the neonates,  $n = 2727$ ). Ranges are attributable to 3 NICUs changing from small to large during the observation period. All NICUs admitting VLBW infants in the state have staff and equipment to provide comprehensive intensive care (including mechanical ventilation) 24 hours per day for even the most immature neonates. Currently there is no formal grading system for level of care in Germany. The effects of different combinations of delivery hospital and NICU volume were analyzed by assigning 1 of the 4 possible combinations to each neonate.

The primary outcome was death before 28 postnatal days, because most deaths among premature infants occur during this period.<sup>4,15,18,19</sup> Gestational age was determined on the basis of early ultrasound scans or the last

**TABLE 1** Maternal and Infant Characteristics of the Study Population (N = 4379)

	No. (%)
Maternal characteristics	
Delivery unit	
≤1000 deliveries per y	1190 (27.2)
>1000 deliveries per y	3189 (72.8)
German	
Yes	3673 (83.9)
No	333 (7.6)
MV <sup>a</sup>	373 (8.5)
Age	
<18 y	46 (1.1)
18–35 y	3795 (86.7)
>35 y	538 (12.3)
Primiparity	
Yes	2497 (57.0)
No	1881 (43.0)
MV	1 (0.02)
Mode of delivery	
Vaginal	592 (13.5)
Cesarean section	3787 (86.5)
Maternal death	
Yes	5 (0.1)
No	4374 (99.9)
Infant characteristics	
NICU	
<36 VLBW admissions per y	1652 (37.7)
≥36 VLBW admissions per y	2727 (62.3)
Inborn	
Yes	2329 (53.2)
No	2050 (46.8)
Gender	
Male	2258 (51.6)
Female	2121 (48.4)
Gestational age	
24 wk	273 (6.2)
25 wk	395 (9.0)
26 wk	504 (11.5)
27 wk	627 (14.3)
28 wk	816 (18.6)
29 wk	898 (20.5)
30 wk	866 (19.8)
Birth weight, median (minimum to maximum), g	1050 (370–1495)
Multiple birth	
No	3107 (71.0)
Twin	1012 (23.1)
Triplet or more	260 (5.9)
Growth status	
SGA	593 (13.5)
Appropriate size for gestational age	3563 (81.4)
Large for gestational age	223 (5.1)
Severe congenital malformations	
Yes	225 (5.1)
No	4154 (94.9)
Death	
<7 d in NICU	341 (7.8)
7–28 d in NICU	137 (3.1)
>28 d in NICU	59 (1.4)

<sup>a</sup> MV indicates missing value.

menstrual period and was recorded as completed weeks. We defined growth status, according to German population-based percentiles, separately for male and female

infants and for singletons and twins.<sup>20</sup> Twin percentiles were used for all multiple births. Birth weight below the 10th percentile was defined as small for gestational age (SGA), between the 10th and 90th percentiles as appropriate weight for gestational age, and above the 90th percentile as large for gestational age. Respiratory distress syndrome was defined as documentation of either this condition or exogenous surfactant administration, because early surfactant application can make the diagnosis of respiratory distress syndrome impossible. Severe congenital malformations were defined according to the Weidtmann code<sup>16</sup> and implied life-threatening characteristics.

### Statistical Analyses

We first calculated Kaplan-Meier survival estimates for infants from small versus large NICUs and compared them by using the log-rank test. Next, we selected, from the 750 variables available as potentially relevant known confounders, those with clinical relevance, those of great interest, and those with potential relevance for accounting for case mixture adjustment (Table 2).

Five-minute Apgar scores were dichotomized on the basis of the established threshold of <7 versus ≥7. The numbers of hospitalization days during pregnancy were categorized, on the basis of the median, as <10 versus ≥10 days, because a linearity assumption did not hold and previous corresponding thresholds were not known. Time since last prenatal steroid treatment was categorized, on the basis of clinically established cutoff points, as ≤24 hours, 2 to 3 days, 4 to 7 days, 8 to 14 days, or >2 weeks.

Univariate analyses used  $\chi^2$ , *t*, and Wilcoxon tests. Variables with *P* values of <.20 in univariate analyses (testing the association with the outcome and with the exposure) were selected for multivariable modeling. Because gestational age affects outcomes strongly, it was included in all analyses, as were gender and multiplicity. Delivery hospital size was included initially in multivariable analyses independent of univariate analysis results.

Multivariable logistic regression analysis was based on general estimating equations. This allows adjustment for clustering, hypothesizing correlation among individuals within units; infants from the same hospital cannot be regarded as independent individuals because of hospital-specific treatment policies.<sup>21,22</sup> Different models were calculated, reducing the significance level from .25 to .10 in stages of .05.<sup>23</sup> Models were considered valid on the basis of the c-statistic and analysis of more-complex models without significant changes.<sup>23</sup> All analyses were performed with SAS 8.02 software (SAS Institute, Cary, NC). In Germany, anonymized secondary data research does not require human research committee review.

**TABLE 2 Potential Confounders Considered in Univariate Analyses**

Maternal Characteristics	Delivery Conditions, Organization/Management	Infant Characteristics
Country of origin	Delivery planned in this unit	Year of birth <sup>a</sup>
Working mother	Pediatrician present at birth <sup>a</sup>	Congenital malformations <sup>a</sup>
Maternal age	Inborn <sup>a</sup>	Gestational age <sup>a</sup>
BMI	Time from birth to NICU admission	Birth weight
Marital status	No. of board-certified neonatologists <sup>a</sup>	SGA <sup>a</sup>
Primiparity <sup>a</sup>		Large for gestational age <sup>a</sup>
Previous stillbirths/abortions/interruptions <sup>a</sup>		Twins <sup>a</sup>
Pregnancy at risk <sup>a</sup>		Triplets or more <sup>a</sup>
Smoking		Gender <sup>a</sup>
Total no. of hospitalization days during pregnancy		5-min Apgar score <sup>a</sup>
Cervix width at admission <sup>a</sup>		Respiratory distress syndrome <sup>a</sup>
Preterm labor <sup>a</sup>		
Premature rupture of membranes/amnion infection syndrome		
Fetal position		
Maternal diabetes		
Preeclampsia/hypertension		
Maternal anemia		
Placental insufficiency <sup>a</sup>		
Cesarean section <sup>a</sup>		
Maternal complications		
Maternal fever		
Maternal death		
Time since last prenatal steroid treatment		

<sup>a</sup> Variables included in the multivariable modeling process.

## RESULTS

In small NICUs, 201 (12.2%) of 1652 infants died within 28 days, compared with 277 (10.2%) of 2727 neonates in large NICUs (crude odds ratio [OR]: 1.23; 95% confidence interval [CI]: 1.01–1.49). Graphs of Kaplan-Meier survival estimates indicated a higher survival rate for infants from large NICUs throughout the first 4 weeks ( $P = .012$ ) (Fig 1).

Variables forced into all multivariable models (gestational age, gender, and multiplicity) and those selected from univariate analyses are indicated in Table 2. Analyzing general estimating equation models by reducing the significance level from .25 to .10 resulted in an adjusted OR of 1.79 (95% CI: 1.21–2.63) for infants treated in small NICUs (Table 3). We considered the model valid on the basis of the c-statistic of 0.823 and analysis of more-complex models without relevant changes in results.

The neonatal mortality was increased by 94% if the infant was born in a small delivery hospital and also was cared for in a small NICU (adjusted OR: 1.94; 95% CI: 1.20–3.14), by 75% if the delivery unit was large but the NICU was small (adjusted OR: 1.75; 95% CI: 1.10–2.78), and by 16% if the delivery hospital was small but the NICU was large (adjusted OR: 1.16; 95% CI: 0.82–1.63) (Fig 2). In models for groups defined by gestational age, with the same initial variables as in previous models, the positive association between small NICU volume and neonatal mortality did not decrease appreciably up to a gestational age of 29 weeks (Table 4).

## DISCUSSION

In this population-based study of the effects of hospital volume on 28-day mortality for VLBW infants (gestational age: 24–30 weeks), the adjusted OR of 1.79 (95% CI: 1.21–2.63) reflects a statistically significant risk increase for neonates from small NICUs (<36 VLBW admissions per year), albeit with a relatively low cutoff value of <36 VLBW admissions per year. Moreover, the adjusted OR for neonatal death was affected more strongly by NICU size than by delivery unit volume for infants admitted to a NICU. A possible cutoff value for future guidelines might be a gestational age of <29 weeks, at which benefits from admission to a large NICU seem to be greatest. This was also suggested recently by both the American Academy of Pediatrics and the German medical authorities.<sup>24,25</sup>

Overall, the neonatal mortality was 10.9%, which was slightly lower than reported by others.<sup>4,10,26,27</sup> This is probably partly attributable to the exclusion of infants who died in the delivery hospital. Moreover, one bias that cannot be controlled for is the lack of information on whether parents had requested a do-not-resuscitate order, which might affect neonatal mortality rates considerably.

Previous studies compared the effects of hospital levels, mainly the delivery units, on different outcome criteria. Levels of care are usually well defined, on the basis of staffing and technical equipment but also neonatal criteria, such as gestational age, multiplicity, or requirement for ventilatory support.<sup>8,19,28</sup> Most studies revealed

FIGURE 1  
Kaplan-Meier survival estimates for  $n = 4379$ , 24–30 weeks.

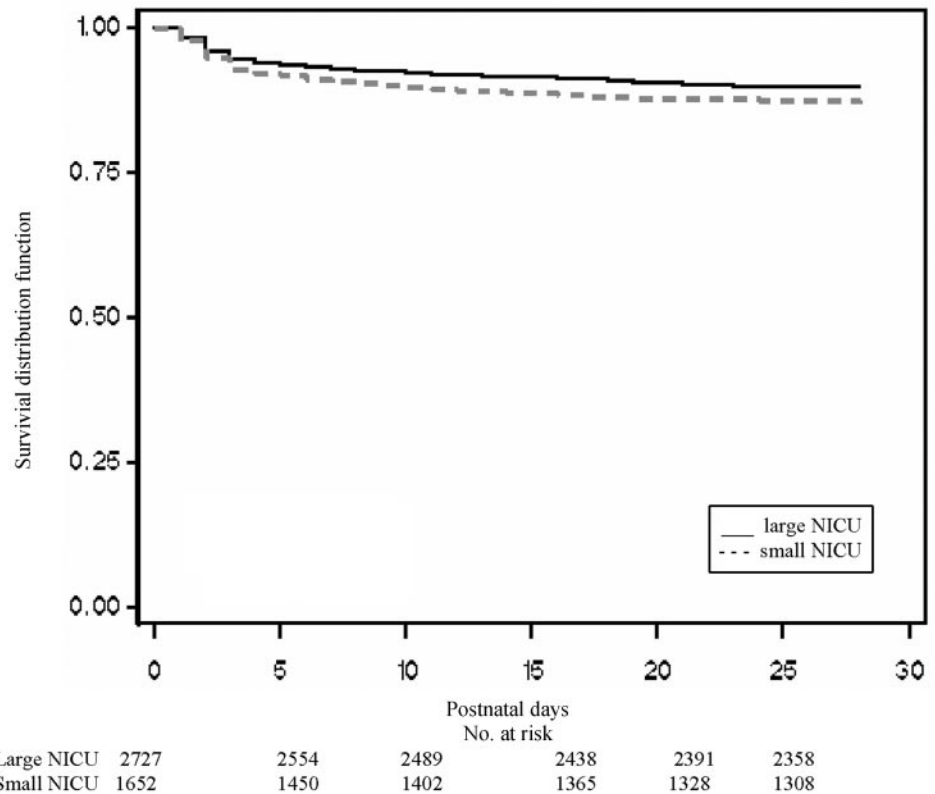


TABLE 3 Adjusted ORs for Neonatal Death of Infants Admitted to a NICU ( $n = 4063$ ; 437 Deceased Infants)

Effect	Adjusted OR	95% CI	P Value
Small NICU	1.79	1.21–2.63	.003
Male	1.62	1.31–2.01	<.0001
Twins	1.50	1.21–1.85	.0002
Triplets or more	1.63	0.72–3.69	.244
Gestational age			
24 wk	32.76	19.63–54.68	<.0001
25 wk	13.27	7.83–22.47	<.0001
26 wk	5.93	3.51–10.01	<.0001
27 wk	4.62	2.77–7.69	<.0001
28 wk	2.41	1.52–7.69	.0002
29 wk	1.72	1.04–2.85	.034
30 wk	1.00		
Congenital malformations	5.62	3.44–9.20	<.0001
SGA	3.56	2.52–5.04	<.0001
Previous stillbirths/abortions/interruptions	0.75	0.55–1.02	.068
Pregnancy at risk	0.75	0.57–1.00	.048
Preterm labor	0.75	0.57–1.02	.062
Inborn	0.81	0.53–1.22	.312
5-min Apgar score of <7	2.95	2.22–3.92	<.0001

significantly increased neonatal mortality for VLBW infants not delivered in level III hospitals, with adjusted ORs ranging from 1.13 to 2.28 for VLBW infants.<sup>6,28–30</sup> Similar results come from comparisons of subspecialty versus nonspecialty perinatal centers<sup>31</sup> and general versus university hospitals.<sup>32</sup>

Studies based on NICU caseloads are sparse, although

they are common for surgical procedures (with caseload being used as an indirect quality measure).<sup>9</sup> Although volume might serve merely as a proxy for other causal factors, satisfactory outcomes are more likely to be achieved in hospitals with substantial caseloads.<sup>33</sup> The discussion about the relationship between delivery service volume and perinatal mortality, however, is already

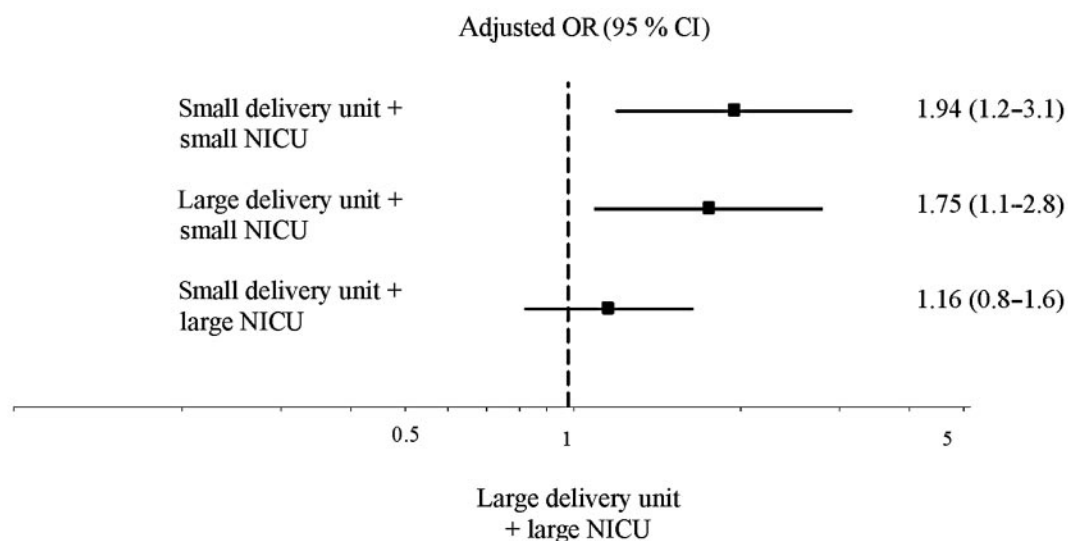


FIGURE 2  
Adjusted ORs and 95% CI for combinations of delivery unit and NICU volume (log scale).

TABLE 4 Adjusted ORs for Neonatal Death in Small Versus Large NICUs, Stratified According to Gestational Age

Gestational Age, wk	No. (No. Deceased)	Adjusted OR <sup>a</sup>	95% CI
24	273 (115)	3.58	1.60–7.97
25	395 (96)	2.43	1.26–4.37
26	504 (67)	1.57	0.73–3.40
27	627 (73)	2.58	1.35–4.94
28	816 (54)	2.23	1.07–4.63
29	891 (42)	0.87	0.49–1.55
30	810 (27)	0.93	0.42–2.03

<sup>a</sup> Adjusted for the following confounders after final variable selection: 24 weeks: gender, multiple birth, SGA; 25 weeks: gender, multiple birth, severe congenital malformations, SGA, 5-minute Apgar score of <7, number of persons with teaching allowance; 26 weeks: gender, multiple birth, severe congenital malformations, SGA, 5-minute Apgar score of <7, primiparity, premature contractions, respiratory distress syndrome; 27 weeks: gender, multiple birth, severe congenital malformations, SGA, 5-minute Apgar score of <7; 28 weeks: gender, multiple birth, severe congenital malformations, SGA, 5-minute Apgar score of <7, number of persons with teaching allowance; 29 weeks: gender, multiple birth, severe congenital malformations, SGA, 5-minute Apgar score of <7, pregnancy at risk; 30 weeks: gender, multiple birth, severe congenital malformations, SGA, 5-minute Apgar score of <7, previous stillbirth/abortion/interruption, cesarean section, cervix width at admission.

>25 years old.<sup>34</sup> Moreover, using daily NICU census as a volume criterion<sup>5,8</sup> might yield different results than using annual VLBW admissions.<sup>35</sup>

In nonfederal Californian hospitals, neonatal mortality was higher in low-volume versus high-volume level III NICUs (adjusted OR: 1.55; 95% CI: 1.22–1.96),<sup>5</sup> which is in keeping with our results. International network data indicate that higher volume seems to be associated with reduced mortality up to a threshold of 50 VLBW admissions per year (95% CI: 41–61 VLBW admissions per year). Below this point, an 11% (95% CI: 5–16%;  $P < .045$ ) reduction in mortality was calculated for every 10 additional infants admitted.<sup>35</sup> In one study, investigators calculated that ~20% of deaths could have

been prevented if 90% of all VLBW infants had been born at the recommended level.<sup>19</sup>

Cifuentes et al<sup>8</sup> investigated neonatal mortality for neonates of <2000 g and found an increased risk in small NICUs, intermediate NICUs, and hospitals without NICUs, in comparison with regional NICUs. They also reported that restriction to VLBW infants would have shown even larger effects, but they considered their results on volume effects as not conclusive.

The United Kingdom Neonatal Staffing Study Group did not find an association between hospital volume and hospital mortality among neonates.<sup>36</sup> However, those analyses were not restricted to VLBW infants, and their study was underpowered to investigate the effect of caseload on mortality risk.

No association between patient volume and mortality has been reported by the Vermont Oxford Network,<sup>37</sup> but the results were criticized for excluding nonparticipating small community hospitals.<sup>31</sup> Moreover, gestational age was not included in the multivariable models.

We found stepwise increasing ORs (Fig 2) for infants from small delivery units and large NICUs (adjusted OR: 1.16), large delivery units but small NICUs (adjusted OR: 1.75), and hospitals where both units were small (adjusted OR: 1.94). Apparently, for infants admitted to a NICU, NICU volume had a larger impact on survival than did the volume of the delivery hospital. If we had included deaths that occurred in the delivery unit, then the effect of delivery unit volume might have been stronger.

The increased mortality risk with decreasing gestational age is well known<sup>15,35</sup> but not linear, as often assumed.<sup>31</sup> Our study is the first to offer separate multivariable models, stratified according to week of gestational age, for the association of hospital volume and

neonatal mortality. This is an elaborate approach yielding relevant confounder insights, for example, gender, severe congenital malformations, and SGA were relevant across all gestational age weeks, whereas other variables were important only for certain gestational age groups. This finding could be of relevance for future gestational age-specific risk studies. A reasonable cutoff value for referral to large perinatal centers seems to be 28 weeks, which was also recommended recently by the American Academy of Pediatrics<sup>25</sup> and German medical authorities.<sup>24</sup>

Other groups reported different influences of hospital volume across birth weight categories.<sup>12,28,31,38</sup> Cifuentes et al<sup>8</sup> reported that, the lower the birth weight, the stronger was the hospital effect. The findings of 2 study groups<sup>31,38</sup> that, within their birth weight cohorts, mortality for neonates with birth weights of 1000 to 1499 g were affected most strongly by low-volume hospitals are intriguing. Overrepresentation of SGA infants with high mortality risk<sup>15</sup> is 1 possible explanation.

Although the increased risk of male infants, infants of multiple births, and infants with severe malformations is in agreement with previous work,<sup>10,39</sup> we could not confirm that infants with severe malformations are preferentially admitted to larger centers (crude OR for small hospitals: 0.80; 95% CI: 0.60–1.06).<sup>40</sup> However, the greater incidence of high-risk pregnancies/infants in large hospitals<sup>12,36</sup> was also obvious in our data. Large NICUs accounted for 68% of infants with gestational ages of  $\leq 27$  weeks, for 75% of all SGA infants, and for 65% of neonates with respiratory distress syndrome. Inborn infants are at decreased mortality risk. One reason why we did not see this effect in our analyses might be that hospital volume and inborn status were correlated strongly. In small NICUs, only 18% of infants were not inborn; in large NICUs, this proportion was 64%. As a result, the adverse effect of having been born in a small hospital would be underestimated.

Several methodologic issues should be considered. We used population-based data. Previous studies were often biased because of the use of non-population-based birth weight cohorts.<sup>35,36</sup> Data from Lower Saxony seem to be representative of other German states,<sup>15</sup> although we acknowledge that a larger sample would have been desirable.

Most previous studies used birth hospital as the primary independent variable.<sup>31,35</sup> Because delivery units and NICUs are often adjacent, different effects are difficult to assess.<sup>7,8</sup> We defined admittance to a NICU as an inclusion criterion because our primary focus was on NICU volume. Moreover, the NICU to which the pediatrician present at birth belonged could not be defined unambiguously. A 1:1 match between delivery hospital and related NICU was not always possible, because some delivery hospitals collaborated with  $\geq 2$  NICUs. This resulted in the exclusion of both fetal deaths and deaths

that occurred in the delivery hospital, potentially introducing a (most likely conservative) bias. The effect of delivery unit volume, including stillbirths and early neonatal deaths, will be the subject of a separate investigation. Another potential source of bias was our decision to assign infants to the NICU in which they were cared for most during their first 1 month of life. Because the sickest infants usually are those transferred to larger centers, our decision likely put the larger hospitals at a disadvantage; however, we preferred this conservative bias to attributing automatically a potentially poor outcome to the initial NICU. In this cohort, only 6% of neonates were transferred. Reanalyzing the models with the initial NICU as the exposure variable changed the results only marginally. The adjusted OR for neonatal death in a small NICU was then 1.82 (95% CI: 1.29–2.59). One potential limitation of our exposure variable is its definition only by hospital volume. We could not differentiate levels of care because all NICUs were equipped to provide comprehensive care for even the most immature neonates, and we did not have detailed information on hospital structure and organization, which should be considered in future studies. These factors, however, are correlated strongly with hospital volume.<sup>5</sup> Also, the volume cutoffs used for both NICUs and delivery hospitals may seem rather low by international standards<sup>10,35</sup> but are indicative of the current situation in Germany. Use of established thresholds, such as 50 VLBW admissions per year,<sup>35</sup> was not possible because, during that time period, only 3 to 5 NICUs fulfilled that criterion. The fact that we still found a volume effect supports the hypothesis of lower neonatal mortality in high-volume hospitals. Our results await confirmation with a more-recent data set and larger volume cutoff values, as well as analyses aimed at determining “optimal” classification cutoff values. We limited our primary outcome to death within 28 days after birth, which happened to comply with other work in this field<sup>4,5,18,19</sup>

We adjusted for case mixture by using prenatal, perinatal, and postnatal confounders.<sup>41,42</sup> In contrast, other retrospective, population-based studies assessed birth and death certificates<sup>28</sup> and thus were incapable of adjusting for the entire spectrum of perinatal confounders. Although physiologic factor-based case mixture adjustment is recommended, such as with Clinical Risk Index for Babies scores,<sup>43</sup> these “baseline” scores might be prone to lead-time bias.<sup>41,44</sup> Clinical Risk Index for Babies data were not complete in our database. As an alternative, we included 5-minute Apgar scores. However, we suggest that a 5-minute Apgar score of  $< 7$  should be considered a correlate and not a cause of increased mortality risk (adjusted OR: 2.95; 95% CI: 2.22–3.92). Case mixture adjustment was strengthened by including maternal characteristics. One interesting finding, although it did not achieve statistical significance after adjustment

for confounders, was that infants of mothers with a cervix width of  $\geq 4$  cm at admission had increased neonatal mortality risk (crude OR: 1.79; 95% CI: 1.40–2.28;  $P < .0001$ ). Obviously, what contributes to a short interval between admission and birth also contributes to increased mortality risk. This finding can be viewed as support for the need for in utero transfer to large perinatal centers.<sup>31</sup>

We adjusted for clustering by using general estimating equation modeling.<sup>22</sup> Neonates from the same hospital are not statistically independent because of their being exposed to equal treatment policies. This issue is often neglected<sup>31,45</sup> and might result in incorrect  $P$  values, incorrect CIs, and bias.<sup>21</sup> To control for collinearity between the factors of previous stillbirths/abortions/interruptions, pregnancy at risk, and preterm labor, we analyzed models with different combinations of these variables, which did not affect the other estimates. Therefore, we decided to keep these potentially correlated variables for face validity reasons and to hold with our a priori fixed methodologic strategy.

## CONCLUSIONS

This is the first population-based study on NICU and delivery unit volume and neonatal mortality among preterm infants that uses sophisticated multivariable data analysis techniques and adjusts for prenatal, perinatal, and postnatal confounders. Neonatal mortality rates were affected more by NICU volume than by delivery volume in this cohort. Survival was best if both the delivery hospital and the NICU were large. Our findings reinforce the need for centralization of perinatal care. A provisional cutoff for transfer to large centers could be impending delivery before 29 weeks of gestation. We encourage future studies, with larger samples and well-defined hospital characteristics, to separate more clearly the different effects of delivery unit and NICU volume.

## ACKNOWLEDGMENT

We are grateful to the Wilhelm Hirte Stiftung (Hannover, Germany) for supporting our work.

## REFERENCES

1. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics*. 1991;87:587–597
2. Goldenberg RL. The prevention of low birthweight and its sequelae. *Prev Med*. 1994;23:627–631
3. Draper ES, Manktelow B, Field DJ, James D. Prediction of survival for preterm births by weight and gestational age: retrospective population based study. *BMJ*. 1999;319:1093–1097
4. Gould JB, Benitz WE, Liu H. Mortality and time to death in very low birth weight infants: California, 1987 and 1993. *Pediatrics*. 2000;105(3). Available at: [www.pediatrics.org/cgi/content/full/105/3/e37](http://www.pediatrics.org/cgi/content/full/105/3/e37)
5. Phibbs CS, Bronstein JM, Buxton E, Phibbs RH. The effects of

- patient volume and level of care at the hospital of birth on neonatal mortality. *JAMA*. 1996;276:1054–1059
6. Yeast JD, Poskin M, Stockbauer JW, Shaffer S. Changing patterns in regionalization of perinatal care and the impact on neonatal mortality. *Am J Obstet Gynecol*. 1998;178:131–135
7. Moster D, Markestad T, Terje Lie R. Assessing quality of obstetric care for low-risk deliveries: methodological problems in the use of population based mortality data. *Acta Obstet Gynecol Scand*. 2000;79:478–484
8. Cifuentes J, Bronstein J, Phibbs CS, Phibbs RH, Schmitt SK, Carlo WA. Mortality in low birth weight infants according to level of neonatal care at hospital of birth. *Pediatrics*. 2002;109:745–751
9. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med*. 2002;137:511–520
10. Horbar JD, Badger GJ, Lewit EM, Rogowski J, Shiono PH. Hospital and patient characteristics associated with variation in 28-day mortality rates for very low birth weight infants: Vermont Oxford Network. *Pediatrics*. 1997;99:149–156
11. Hodgson DC, Zhang W, Zaslavsky AM, Fuchs CS, Wright WE, Ayanian JZ. Relation of hospital volume to colostomy rates and survival for patients with rectal cancer. *J Natl Cancer Inst*. 2003;95:708–716
12. Gortmaker S, Sobol A, Clark C, Walker DK, Geronimus A. The survival of very low-birth weight infants by level of hospital of birth: a population study of perinatal systems in four states. *Am J Obstet Gynecol*. 1985;152:517–524
13. Jonsson B, Katz-Salamon M, Faxelius G, Broberger U, Lagercrantz H. Neonatal care of very-low-birthweight infants in special-care units and neonatal intensive-care units in Stockholm: early nasal continuous positive airway pressure versus mechanical ventilation: gains and losses. *Acta Paediatr Suppl*. 1997;419:4–10
14. Arnold CC, Kramer MS, Hobbs CA, McLean FH, Usher RH. Very low birth weight: a problematic cohort for epidemiologic studies of very small or immature neonates. *Am J Epidemiol*. 1991;134:604–613
15. Bartels D, Kreienbrock L, Dammann O, Wenzlaff P, Poets CF. Population-based study on the outcome of small for gestational age newborns. *Arch Dis Child Fetal Neonatal Ed*. 2005;90:F53–F59
16. Center for Quality Management. *NPEXtra 1996*. Hannover, Germany: Druckerei L. Lindenhain; 1997
17. Bartels D, Kreienbrock L, Wenzlaff P, Poets CF. Can data from a neonatal quality control program be used for epidemiologic studies? *Pediatr Res*. 2002;52:781
18. Sankaran K, Chien LY, Walker R, Seshia M, Ohlsson A. Variations in mortality rates among Canadian neonatal intensive care units. *CMAJ*. 2002;166:173–178
19. Samuelson JL, Buehler JW, Norris D, Sadek R. Maternal characteristics associated with place of delivery and neonatal mortality rates among very-low-birthweight infants, Georgia. *Paediatr Perinat Epidemiol*. 2002;16:305–313
20. Voigt M, Schneider KT, Jahrig K. Analysis of a 1992 birth sample in Germany, I: new percentile values of the body weight of newborn infants [in German]. *Geburtshilfe Frauenheilkd*. 1996;56:550–558
21. Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. *Ann Intern Med*. 2001;135:112–123
22. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988;44:1049–1060

23. Hosmer D, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons; 1989
24. German Federal Ministry of Health and Social Welfare. *Declaration on Measures of Quality Assurance in the Care of Premature and Mature Neonates* [in German]. Berlin, Germany: German Federal Ministry of Health and Social Welfare; 2005
25. Stark AR, Couto J. Levels of neonatal care. *Pediatrics*. 2004;114:1341–1347
26. Murphy DJ, Hope PL, Johnson A. Neonatal risk factors for cerebral palsy in very preterm babies: case-control study. *BMJ*. 1997;314:404–408
27. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. *Pediatrics*. 2001;107(1). Available at: [www.pediatrics.org/cgi/content/full/107/1/e1](http://www.pediatrics.org/cgi/content/full/107/1/e1)
28. Bode MM, O'Shea TM, Metzguer KR, Stiles AD. Perinatal regionalization and neonatal mortality in North Carolina, 1968–1994. *Am J Obstet Gynecol*. 2001;184:1302–1307
29. Sanderson M, Sappenfield WM, Jespersen KM, Liu Q, Baker SL. Association between level of delivery hospital and neonatal outcomes among South Carolina Medicaid recipients. *Am J Obstet Gynecol*. 2000;183:1504–1511
30. Menard MK, Liu Q, Holgren EA, Sappenfield WM. Neonatal mortality for very low birth weight deliveries in South Carolina by level of hospital perinatal service. *Am J Obstet Gynecol*. 1998;179:374–381
31. Warner B, Musial MJ, Chenier T, Donovan E. The effect of birth hospital type on the outcome of very low birth weight infants. *Pediatrics*. 2004;113:35–41
32. Johansson S, Montgomery SM, Ekblom A, et al. Preterm delivery, level of care, and infant death in Sweden: a population-based study. *Pediatrics*. 2004;113:1230–1235
33. Farley DE, Ozminkowski RJ. Volume-outcome relationships and in-hospital mortality: the effect of changes in volume over time. *Med Care*. 1992;30:77–94
34. Williams RL. Measuring the effectiveness of perinatal medical care. *Med Care*. 1979;17:95–110
35. Rogowski JA, Horbar JD, Staiger DO, Kenny M, Carpenter J, Geppert J. Indirect vs direct hospital quality indicators for very low-birth-weight infants. *JAMA*. 2004;291:202–209
36. United Kingdom Neonatal Staffing Study Group. Patient volume, staffing, and workload in relation to risk-adjusted outcomes in a random stratified sample of UK neonatal intensive care units: a prospective evaluation. *Lancet*. 2002;359:99–107
37. Horbar JD. The Vermont Oxford Network: evidence-based quality improvement for neonatology. *Pediatrics*. 1999;103(suppl E):350–359
38. Powell SL, Holt VL, Hickok DE, Easterling T, Connell FA. Recent changes in delivery site of low-birth-weight infants in Washington: impact on birth weight-specific mortality. *Am J Obstet Gynecol*. 1995;173:1585–1592
39. Lagercrantz H, Katz-Salamon M, Forsberg H. The Stockholm Neonatal Project: neonatal mortality and morbidity at the Children's Centre, Karolinska Hospital. *Acta Paediatr Suppl*. 1997;419:11–15
40. Mehta S, Atherton HD, Schoettker PJ, Hornung RW, Perlstein PH, Kotagal UR. Differential markers for regionalization. *J Perinatol*. 2000;20:366–372
41. Richardson DK, Tarnow-Mordi WO, Escobar GJ. Neonatal risk scoring systems: can they predict mortality and morbidity? *Clin Perinatol*. 1998;25:591–611
42. Richardson DK, Phibbs CS, Gray JE, McCormick MC, Workman-Daniels K, Goldmann DA. Birth weight and illness severity: independent predictors of neonatal mortality. *Pediatrics*. 1993;91:969–975
43. International Neonatal Network. The CRIB (Clinical Risk Index for Babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. *Lancet*. 1993;342:193–198
44. Richardson DK, Gray JE, McCormick MC, Workman K, Goldmann DA. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. *Pediatrics*. 1993;91:617–623
45. Moster D, Lie RT, Markestad T. Relation between size of delivery unit and neonatal death in low risk deliveries: population based study. *Arch Dis Child Fetal Neonatal Ed*. 1999;80:F221–F225

## Hospital Volume and Neonatal Mortality Among Very Low Birth Weight Infants

Dorothee B. Bartels, David Wypij, Paul Wenzlaff, Olaf Dammann and Christian F. Poets

*Pediatrics* 2006;117:2206-2214

DOI: 10.1542/peds.2005-1624

**This information is current as of June 24, 2006**

<b>Updated Information &amp; Services</b>	including high-resolution figures, can be found at: <a href="http://www.pediatrics.org/cgi/content/full/117/6/2206">http://www.pediatrics.org/cgi/content/full/117/6/2206</a>
<b>References</b>	This article cites 39 articles, 18 of which you can access for free at: <a href="http://www.pediatrics.org/cgi/content/full/117/6/2206#BIBL">http://www.pediatrics.org/cgi/content/full/117/6/2206#BIBL</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Premature &amp; Newborn</b> <a href="http://www.pediatrics.org/cgi/collection/premature_and_newborn">http://www.pediatrics.org/cgi/collection/premature_and_newborn</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.pediatrics.org/misc/Permissions.shtml">http://www.pediatrics.org/misc/Permissions.shtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.pediatrics.org/misc/reprints.shtml">http://www.pediatrics.org/misc/reprints.shtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

