Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009

AUTHORS: Jeffrey D. Horbar, MD,[a,b] Joseph H. Carpenter, MS,[b] Gary J. Badger, MS,[c] Michael J. Kenny, MS,[c] Roger F. Soll, MD,[a,b] Kate A. Morrow, MS,[b] and Jeffrey S. Buzas, PhD[b,d]

Departments of [a]Pediatrics, [c]Medical Biostatistics, and [d]Mathematics and Statistics, University of Vermont, Burlington, Vermont; and [b]Vermont Oxford Network, Burlington, Vermont

KEY WORDS
very low birth weight, mortality, morbidity, Vermont Oxford Network

ABBREVIATIONS
CI—confidence interval
CLD—chronic lung disease
IVH—intraventricular hemorrhage
NEC—necrotizing enterocolitis
NICHD—Eunice Kennedy Shriver National Institute of Child Health and Human Development
PVL—periventricular leukomalacia
ROP—retinopathy of prematurity
VLBW—very low birth weight

Each of the authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; participated in drafting the article or revising it critically for important intellectual content; and gave final approval of the version to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3028

doi:10.1542/peds.2011-3028

Accepted for publication Feb 16, 2012

Address correspondence to Jeffrey D. Horbar, MD, Professor of Pediatrics, University of Vermont, Chief Executive and Scientific Officer of Vermont Oxford Network, 33 Kilburn St, Burlington, VT 05401. E-mail: horbar@vtoxford.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *Drs Buzas, Horbar, Soll, Mr Carpenter, and Ms Morrow are employees of the Vermont Oxford Network; Mr Badger and Mr Kenny have indicated they have no financial relationships relevant to this article to disclose.*

FUNDING: No external funding.

COMPANION PAPER: A companion to this article can be found on page 1164, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2012-0795.

WHAT'S KNOWN ON THIS SUBJECT: Infants weighing 501 to 1500 g are at high risk for mortality and for neonatal morbidities associated with both short- and long-term adverse consequences.

WHAT THIS STUDY ADDS: Mortality and major neonatal morbidity in survivors decreased for infants 501 to 1500 g between 2000 and 2009. However, in 2009, a high proportion of these infants still either died or survived after experiencing ≥1 major neonatal morbidity.

abstract

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OBJECTIVE: To identify changes in mortality and neonatal morbidities for infants with birth weight 501 to 1500 g born from 2000 to 2009.

METHODS: There were 355 806 infants weighing 501 to 1500 g who were born in 2000–2009. Mortality during initial hospitalization and major neonatal morbidity in survivors (early and late infection, chronic lung disease, necrotizing enterocolitis, severe retinopathy of prematurity, severe intraventricular hemorrhage, and periventricular leukomalacia) were assessed by using data from 669 North American hospitals in the Vermont Oxford Network.

RESULTS: From 2000 to 2009, mortality for infants weighing 501 to 1500 g decreased from 14.3% to 12.4% (difference, −1.9%; 95% confidence interval, −2.3% to −1.5%). Major morbidity in survivors decreased from 46.4% to 41.4% (difference, −4.9%; 95% confidence interval, −5.6% to −4.2%). In 2009, mortality ranged from 36.6% for infants 501 to 750 g to 3.5% for infants 1251 to 1500 g, whereas major morbidity in survivors ranged from 82.7% to 18.7%. In 2009, 49.2% of all very low birth weight infants and 89.2% of infants 501 to 750 g either died or survived with a major neonatal morbidity.

CONCLUSIONS: Mortality and major neonatal morbidity in survivors decreased for infants with birth weight 501 to 1500 g between 2000 and 2009. However, at the end of the decade, a high proportion of these infants still either died or survived after experiencing ≥1 major neonatal morbidity known to be associated with both short- and long-term adverse consequences. *Pediatrics* 2012;129:1019–1026

Very low birth weight (VLBW) infants (those weighing <1500 g at birth) represent 1.5% of live births, yet account for >50% of infant deaths in the United States.[1] Surviving VLBW infants are at high risk for neurodevelopmental disabilities and generate substantial costs for their families and society.[2,3] Many VLBW infants experience major morbidities during their initial hospitalization, including bloodstream and central nervous system infections, necrotizing enterocolitis (NEC), chronic lung disease (CLD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP). These morbidities expose infants to additional diagnostic, therapeutic, and surgical interventions; cause psychological distress for families; and increase length of stay, the risk of rehospitalization, and costs.[4–9] They are associated with later neurodevelopmental disabilities including cerebral palsy, cognitive delay, hearing loss, and visual impairment.[10–18]

Mortality and neonatal morbidity for VLBW infants declined substantially in the early 1990s before leveling off for the remainder of the decade.[19–21] We undertook this study to identify changes in mortality and major neonatal morbidity for infants with birth weight 501 to 1500 g born between 2000 and 2009 and to provide up-to-date estimates of the rates with which these outcomes occur.

METHODS

Participants submitted deidentified data for infants born at their hospitals or transferred to them within 28 days of birth.[22] This study was restricted to infants weighing 501 to 1500 g. Data, collected by local staff using uniform definitions, were submitted to the Vermont Oxford Network. Records were subjected to automated checks for quality and completeness and returned for correction if needed. The Committee on Human Research at the University of Vermont approved the use of the database for research.

Mortality was defined as death before discharge. Infants transferred from the reporting hospital to another hospital were tracked for survival status until discharge from the hospital.

Infants were classified as having a major neonatal morbidity if they had ≥1 of the following conditions before discharge from the reporting hospital: early bacterial infection, late bacterial or fungal infection, NEC, CLD, severe IVH, PVL, or severe ROP.

Early bacterial infection was defined as recovery of a bacterial pathogen from blood or cerebrospinal fluid obtained within 3 days of birth. Late bacterial infection included recovery of either coagulase-negative *Staphylococcus* or other bacterial pathogen from blood or cerebrospinal fluid obtained >3 days after birth. Diagnosis of coagulase-negative staphylococcal infection also required systemic signs of infection and treatment for ≥5 with intravenous antibiotics. Fungal infection was defined as recovery of a fungus from a blood specimen obtained >3 days after birth.

The diagnosis of NEC required ≥1 clinical sign (eg, bilious gastric aspirate or emesis, abdominal distention, gross or occult blood in the stool) and ≥1 radiographic finding (eg, pneumatosis intestinalis, hepatobiliary gas, pneumoperitoneum).

Infants were classified as having CLD if they received supplemental oxygen at 36 weeks' postmenstrual age. Infants discharged before 36 weeks were classified based on their oxygen status at discharge.[23]

IVH was diagnosed with cranial imaging within 28 days of birth by using cranial ultrasound (2000–2005) or cranial ultrasound, MRI, or computed tomography scan (2006–2009). Severe IVH was defined as grades 3 and 4.[24] PVL was defined as the presence of periventricular cysts on cranial ultrasound. The diagnosis and staging of ROP were based on retinal examination before discharge with severe ROP defined as stages 3 to 5.[25]

The significance of changes over time in outcomes was evaluated by using logistic regression with birth year represented as a categorical variable. To adjust for case-mix, race/ethnicity (Hispanic, black [non-Hispanic], white [non-Hispanic], other [non-Hispanic]), gender, gestational age, location of birth (inborn, outborn), multiple birth, small size for gestational age, birth defect, and 1-minute Apgar score were included as covariates in the model. These covariates were chosen because of their association with outcomes and their inclusion in models used for risk adjusted reporting to network members over the study period. Eligible infants from multiple births were included as separate observations. Small size for gestational age was defined within categories based on gender, race/ethnicity, and multiple birth as birth weight below the 10th percentile based on smoothed curves from the US Natality Dataset.[26] A contrast was constructed to test for a linear trend in rates across years. Standardized rates and the differences in these rates between 2000 and 2009 were derived from the logistic model with characteristics of infants born in 2009 defining the reference population. Analyses based on standardized rates computed by using infants born in 2000 as the reference population were consistent with those using 2009 (data not presented). Confidence intervals (CIs) for the differences in rates were computed based on SEs by using the Delta method. All analyses accounted for clustering of infants within hospital by using generalized estimating equations.[27] Additional analyses were performed within

250-g birth weight categories. To evaluate the potential effect of changes in participating hospitals over time, primary analyses were replicated for the 278 hospitals that participated for all 10 years. Analyses were performed by using SAS Statistical Software Version 9.2 (SAS Institute, Cary, NC).

RESULTS

Hospitals and Infants

Six hundred sixty-nine North American hospitals participated in the Vermont Oxford Network from 2000 to 2009 (Supplemental Table 5). Of these hospitals, 33.8% were type A NICUs (ie, restriction on infants they could ventilate), 49.4% were type B NICUs (ie, no restrictions on ventilation, neonatal surgery except open heart surgery), and 16.8% were type C NICUs (ie, no restrictions on ventilation, neonatal surgery including open heart surgery). Half of these participated for ≥8 years; 75% participated for ≥4 years; and 42% participated for all 10 years. Thirty-six percent were teaching hospitals. The median annual number of VLBW infants per hospital was 57 (interquartile range 30–103).

A total of 355 806 infants with birth weight 501 to 1500 g were cared for at the 669 hospitals from 2000 to 2009. Infant characteristics remained stable throughout the study period with the exception of race, ethnicity, and birth defects. From 2000 to 2009, the distribution by race and ethnicity changed significantly (black, 27.2%–29.4%; Hispanic, 15.5%–18.4%; white, 52.3%–45.7%; other, 5.0%–6.5%; $P < .001$). The rate of birth defects increased from 4.3% in 2000 to 5.1% in 2009 ($P = .004$). There were no significant changes in other infant characteristics. Overall, 51.1% of the infants were male, 27.8% were multiple births, and 19.0% were small for gestational age. Infants with Apgar scores of ≤3 at 1 minute represented 25.3% of all infants. Average birth weight in 2000 was 1049 g compared with 1055 g in 2009. The mean gestational age was 28.1 weeks in both 2000 and 2009. The percentages of infants in the 4 birth weight categories were 501 to 750 g, 19.9%; 751 to 1000 g, 23.3%; 751 to 1000 g, 25.8%; and 1251 to 1500 g, 31.0%.

Mortality

From 2000 to 2009 there were significant decreasing trends in the observed mortality rate for infants weighing 501 to 1500 g and within each 250-g birth weight category except the highest, 1251 to 1500 g (Table 1). Mortality rates in all years were highest for infants weighing 501 to 750 g and decreased with increasing birth weight.

The standardized mortality rate for infants weighing 501 to 1500 g decreased from 14.3% in 2000 to 12.4% in 2009 (difference, −1.9%; 95% CI, −2.3% to −1.5%) (Table 2). The change in mortality was greatest for infants 501 to 750 g (difference, −5.3%; 95% CI, −6.7% to −3.8%) and became smaller with increasing birth weight. In 2009, the mortality rate for infants 501 to 750 g was 36.6% compared with 11.7% for infants 751 to 1000 g, 5.7% for infants 1001 to 1250 g, and 3.5% for infants 1251 to 1500 g.

Major Neonatal Morbidity

There were significant decreasing trends in the observed rate of major neonatal morbidity in survivors for all birth weight categories (Table 3). The observed rates of major neonatal morbidity in survivors were highest in all years for infants weighing 501 to 750 g and decreased with increasing birth weight.

The standardized rate of major neonatal morbidity in survivors for infants 501 to 1500 g decreased from 46.4% in 2000 to 41.4% in 2009 (difference, −4.9%; 95% CI, −5.6% to −4.2%) (Table 4). The change was smallest for infants 501 to 750 g (difference, −1.8%; 95% CI, −3.4% to −0.3%), and ranged from −4.6% to −5.7% in the other birth weight categories. In 2009, the rates of major neonatal morbidity in survivors for infants 501 to 750 g was 82.7% compared with 57.4% for infants 750 to 1000 g, 33.1% for infants 1001 to 1250 g, and 18.7% for infants 1251 to 1500 g.

There were statistically significant decreases from 2000 to 2009 in the rates of several individual major neonatal morbidities for surviving infants weighing 501 to 1500 g including early infection, late infection, CLD, and severe ROP (Table 4). The decreases in severe IVH and PVL were of borderline statistical significance, as was the increase in the rate of NEC.

TABLE 1 Observed Mortality Rates by Year and Birth Weight Category for Infants 501 to 1500 g From 2000 to 2009 ($N = 355\,806$)[a]

Weight, g	2000, % $n = 27\,125$	2001, % $n = 27\,498$	2002, % $n = 29\,352$	2003, % $n = 31\,476$	2004, % $n = 34\,772$	2005, % $n = 37\,227$	2006, % $n = 39\,854$	2007, % $n = 41\,653$	2008, % $n = 43\,283$	2009, % $n = 43\,566$	*P* Value[a]
All 501–1500	14.1	14.3	15.0	14.4	14.2	14.0	13.9	13.7	12.9	12.5	<.001
501–750	41.7	43.1	44.0	42.2	43.2	41.2	41.5	39.8	39.2	36.6	<.001
751–1000	13.0	13.3	13.9	14.5	13.5	13.5	13.4	13.8	12.6	11.7	<.001
1001–1250	6.3	5.9	5.8	5.9	5.4	6.0	5.4	5.9	5.3	5.7	<.001
1251–1500	3.5	3.4	3.8	3.6	3.3	3.5	3.9	3.4	3.3	3.5	.112

Mortality data were missing for 0.3% of infants.

[a] *P* values correspond to the test for linear trend across years, after adjusting for infant characteristics by using logistic regression.

TABLE 2 Comparison of Standardized Rates for Mortality in 2000 and 2009 for Infants 501 to 1500 g

	2000, %	2009, %	Difference (95% CI)
All 501–1500 g	14.3	12.4	−1.9 (−2.3 to −1.5)
501–750 g	41.8	36.6	−5.3 (−6.7 to −3.8)
751–1000 g	13.8	11.7	−2.2 (−3.2 to −1.2)
1001–1250 g	6.4	5.7	−0.7 (−1.4 to −0.1)
1251–1500 g	3.7	3.5	−0.2 (−0.7 to 0.2)

Adjusted for infant characteristics based on logistic regression. Values are computed by using the characteristics of infants born in 2009 as the reference population.

Death or Major Neonatal Morbidity

The combined outcome of death or ≥1 major neonatal morbidity in survivors, among all infants 501 to 1500 g, decreased from 53.8% in 2000 to 49.2% in 2009 (difference, −4.6%; 95% CI, −5.3% to −4.0%). The rates of the combined outcome were highest for infants weighing 501 to 750 g and decreased with increasing birth weight. The rates decreased significantly from 2000 to 2009 in all birth weight categories with changes of −1.6% (95% CI,−2.6% to −0.6%) in the 501 to 750 g category and −5.5% (95% CI, −6.9% to −4.2%), −5.6% (95% CI, −7.0% to −4.2%), and −4.6% (95% CI, −5.8% to −3.5%) in the 751 to 1000 g, 1001 to 1250 g, and 1251 to 1500 g categories, respectively (Fig 1). In 2009, the rates of the combined outcome of death or major neonatal morbidity in survivors was 89.2% for infants weighing 501 to 750 g compared with 62.6% for infants 751 to 1000 g, 37.1% for infants 1001 to 1250 g, and 21.8% for infants 1251 to 1500 g.

The primary analyses were replicated for the 278 hospitals that participated in all 10 years of the study. The results of these analyses parallel the results from all 669 hospitals. For these hospitals, the estimated changes in mortality (−2.1%; 95% CI, −2.6% to −1.6%), major neonatal morbidity in survivors (−5.3%; 95% CI, −6.1% to −4.5%), and the combined outcome of mortality or major neonatal morbidity in survivors (−5.0%; 95% CI, −5.8% to −4.3%) were consistent with those from the full sample.

DISCUSSION

Between 2000 and 2009, the rates of mortality and major neonatal morbidities in survivors decreased for infants with a birth weight of 501 to 1500 g. As a consequence, the percentage of these infants with an unfavorable outcome defined as either dying or experiencing ≥1 major neonatal morbidity decreased by 4.6%. This indicates that for every 22 infants weighing 501 to 1500 g who were cared for in 2009, 1 fewer infant would have had an unfavorable outcome compared with similar infants cared for in 2000. Infants weighing 501 to 750 g had the largest decrease in mortality but the smallest decrease in survival with morbidity. The 5.3% decrease in mortality before discharge from 2000 to 2009 we observed for infants 501 to 750 g is consistent with the 4.6% decrease in infant mortality from 2000 to 2007 reported

TABLE 3 Observed Major Morbidity Rates by Year for Surviving Infants 501 to 1500 g From 2000 to 2009 (*N* = 305 770)

	2000, % *n* = 23 248	2001, % *n* = 23 493	2002, % *n* = 24 903	2003, % *n* = 26 872	2004, % *n* = 29 742	2005, % *n* = 31 912	2006, % *n* = 34 186	2007, % *n* = 35 822	2008, % *n* = 37 575	2009, % *n* = 38 017	*P* Value[a]
Any major morbidity[b]											
All 501–1500 g	45.8	47.2	46.9	46.6	45.9	46.0	45.2	44.0	42.1	41.4	<.001
501–750 g	84.0	87.7	85.7	87.0	86.2	86.5	85.8	84.5	84.0	82.7	<.001
751–1000 g	62.1	65.4	64.5	65.1	64.8	63.3	62.9	61.2	59.7	57.4	<.001
1001–1250 g	38.7	39.2	39.4	39.3	38.3	38.7	38.1	36.3	34.2	33.1	<.001
1251–1500 g	23.4	24.3	23.7	23.1	22.8	22.5	21.7	20.8	19.3	18.7	<.001
Major neonatal morbidities											
Early bacterial infection	1.9	1.8	1.9	1.6	1.8	1.8	1.7	1.6	1.6	1.7	.074
Late infection (bacterial or fungal)[c]	21.1	20.6	19.7	20.4	20.5	19.9	19.1	18.4	16.9	15.0	<.001
NEC	4.8	4.7	4.6	5.0	4.7	5.5	5.7	6.1	5.8	5.3	<.001
CLD[d]	27.1	30.0	30.4	29.8	28.3	28.9	28.8	27.7	26.2	26.2	<.001
Severe IVH (grades 3 and 4)[e]	6.2	6.2	6.6	6.6	6.5	6.4	6.6	6.3	6.3	6.1	.044
PVL[f]	3.0	3.2	2.9	2.9	2.8	2.9	3.1	2.9	2.8	2.7	.019
Severe ROP (stages 3–5) [g]	10.5	11.4	10.9	10.8	9.9	9.5	8.3	8.0	7.5	6.8	<.001

Sample sizes vary across outcome measures. Less than 1% of cases have missing data for any measure unless otherwise noted.

[a] *P* values correspond to the test for linear trend across years, after adjusting for infant characteristics by using logistic regression.

[b] Data were missing for 5.5% of surviving infants.

[c] Among surviving infants in the reporting hospital after day 3 of life, *N* = 304 615.

[d] Among infants with gestational age of ≤36 wk, *N* = 304 918.

[e] Among infants who received cranial imaging within 28 d of birth, *N* = 288 341.

[f] Among infants who received cranial imaging before discharge, *N* = 292 080.

[g] Among infants who received an eye exam before discharge, *N* = 236 580.

TABLE 4 Comparison of Standardized Rates for Major Neonatal Morbidities in 2000 and 2009 for Surviving Infants 501 to 1500 g

	2000, %	2009, %	Difference (95% CI)
Any major morbidity			
All 501–1500 g	46.4	41.4	−4.9 (−5.6 to −4.2)
501–750 g	84.5	82.7	−1.8 (−3.4 to −0.3)
751–1000 g	63.1	57.4	−5.6 (−7.2 to −4.1)
1001–1250 g	38.8	33.1	−5.7 (−7.1 to −4.3)
1251–1500 g	23.3	18.7	−4.6 (−5.8 to −3.5)
Major neonatal morbidities			
Early bacterial infection	2.0	1.7	−0.3 (−0.6 to −0.1)
Late infection (bacterial or fungal)	21.5	15.0	−6.6 (−7.2 to −6.0)
NEC	4.9	5.3	0.4 (0.0 to 0.7)
CLD	27.7	26.3	−1.4 (−2.1 to −0.8)
Severe IVH (grades 3 and 4)	6.5	6.1	−0.4 (−0.8 to 0.0)
PVL	3.0	2.7	−0.3 (−0.6 to −0.0)
Severe ROP (stages 3–5)	10.2	6.8	−3.3 (−3.8 to −2.8)

Adjusted for infant characteristics based on logistic regression. Values are computed by using the characteristics of infants born in 2009 as the reference population.

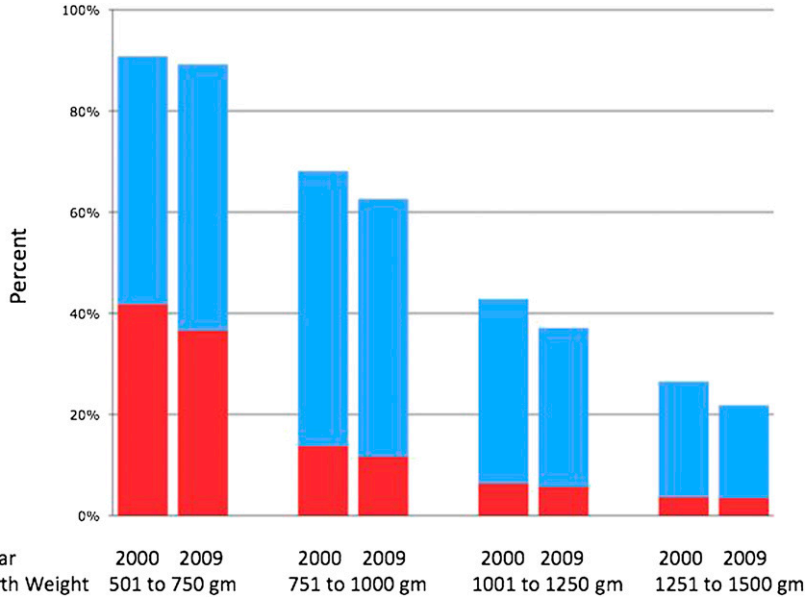

FIGURE 1
Mortality and major neonatal morbidity in survivors in 2009 compared with 2000 by birth weight category for infants 501 to 1500 g. Mortality (red bar) and major neonatal morbidity in survivors (blue bar) by 250-g birth weight category in 2000 and 2009. The total height of the bar represents the percentage of infants who either died or survived with ≥1 more major neonatal morbidity.

for infants 500 to 749 g in the United States.[1]

Despite the improvements in outcomes between 2000 and 2009, 49% of all infants with birth weight 501 to 1500 g and 89% of those with birth weight 501 to 750 g either died or survived after experiencing ≥1 major neonatal morbidity in 2009. Mortality rates in 2009 ranged from 36.6% for infants of 501 to 750 g to 3.5% for infants of 1251 to 1500 g. Rates of major neonatal morbidity in survivors ranged from 82.7% for infants of 501 to 750 g to 18.7% for infants of 1251 to 1500 g. These estimates provide up-to-date information on mortality and morbidity for infants of 501 to 1500 g cared for in a wide range of NICUs caring for >80% of the infants in this birth weight category born in North America in 2009.[28–30]

We evaluated changes in mortality and major neonatal morbidity for the entire decade of 2000–2009. Two other North American neonatal networks have reported findings from periods overlapping the one we studied. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network reported on 9575 surviving infants of 22 to 28 weeks' gestation born at 1 of 20 participating hospitals.[31] After adjusting for case mix, they found a small but statistically significant increase between 2003 and 2007 in the proportion of infants surviving without a major neonatal morbidity (37% in 2003, 36% in 2007; adjusted relative risk, 1.04; 95% CI 1.02–1.06) but did not find any decrease in mortality (28% in both 2003 and 2007; adjusted relative risk, 1.00; 95% CI, 0.99–1.01). We included the same major morbidities as the NICHD in our definition, but our study population included infants of more advanced gestational age.

The Canadian Neonatal Network reported outcomes for 3763 infants of <29 weeks' gestation treated in 1996–1997 and 2006–2007 at 15 Canadian hospitals.[32] Mortality for these infants decreased from 17.2% to 14.7% over this period (adjusted odds ratio, 1.13; 95% CI 0.92–1.40), whereas bronchopulmonary dysplasia defined as oxygen or pressure support at 36 weeks' postmenstrual age increased from 34.7% to 46.1% (adjusted odds ratio, 1.88; 95% CI 1.60–2.20). This contrasts with our finding of statistically significant decreases in both mortality and in the rate of CLD defined as supplemental oxygen at 36 weeks.

A population-based study of 1011 infants born in Sweden before 27 weeks' gestation from 2004 to 2007 found that 55% of 1-year survivors had experienced ≥1 major morbidity.[33] As opposed to our study and the NICHD study, infection was not included as a major

morbidity. The different periods and patient populations make comparisons of the estimates of mortality and morbidity in survivors among our study and those from the NICHD, Canada, and Sweden difficult. However, all 3 studies found that a substantial percentage of surviving infants at the lowest ranges of birth weight and gestational age experienced ≥1 major neonatal morbidity during their initial hospitalization.

This is concerning for two reasons. First, these morbidities are significant adverse events in their own right, complicating the NICU course; exposing infants to additional diagnostic, therapeutic, and surgical interventions; causing psychological distress for families; and increasing length of stay, the risk of rehospitalization, and costs.[4–9]

Second, the major neonatal morbidities are predictive of long-term neurodevelopmental disabilities such as cerebral palsy, cognitive delay, hearing loss, and visual impairment.[10–18] We can estimate the risks for long-term neurodevelopmental disabilities by using the results of Schmidt et al, who reported that 3 neonatal morbidities (CLD, brain injury [severe IVH and PVL], and severe ROP) strongly predict adverse neurodevelopmental outcome (cerebral palsy, cognitive delay, severe hearing loss, bilateral blindness) at 18 months of age for infants with birth weights of 500 to 999 g.[10] They estimated the risk of poor outcome to be 18% for infants with none of the 3 morbidities and 42%, 62%, and 88% for infants with 1, 2, and 3 morbidities, respectively. If we apply the Schmidt score to our population of infants of 501 to 1000 g born in 2009, this translates into an overall estimated risk of 36% for later neurodevelopmental disabilities for these infants, a risk similar to that reported in 2-year follow-up studies of a cohort of extremely low birth weight infants at Vermont Oxford Network centers from 1998 to 2003.[34] Neonatal infection and NEC, which many of the infants in our study also experienced, have been shown to additionally increase the risk of later neurodevelopmental impairment.[35,36]

It would not be appropriate to estimate the risk of later neurodevelopmental disabilities for the infants >1000 g by using the Schmidt score since the score has not been validated in that population. However, the rates of major neonatal morbidity in survivors of 33% for infants 1001 to 1250 g and 19% for infants 1251 to 1500 g suggest that many of these infants are at risk as well. Given that mortality rates for VLBW infants >1000 g are currently in the range of 5%, opportunities for improvement in this group will be in additional reduction in the rates of major neonatal morbidities. For VLBW infants weighing ≤1000 g, there are opportunities for improvement in both mortality and major morbidity.

There are several limitations to our study. Eligibility was restricted to infants with a birth weight of 501 to 1500 g. Thus, our inferences are limited to infants in that weight range. We did not define or stratify our study population based on gestational age because before 2006, eligibility for the Vermont Oxford Network Database was based only on birth weight. A previous report from the Vermont Oxford Network of infants of 401 to 500 g born from 1996 to 2000 found that 17% of the infants survived to discharge with few surviving without major morbidity.[37] Additional studies focusing on infants at the lowest ranges of birth weight and gestational age are warranted. Infants who were transferred to another hospital were only followed for the development of a major morbidity until they were discharged from the reporting hospital. This limitation does not apply to mortality since survival status was tracked for transferred infants until they were discharged from the hospital. Since infants who transferred for reasons other than discharge planning and did not have a major morbidity before their transfer represented 1.0% and 1.1% of infants in 2000 and 2009, respectively, it is unlikely that our estimates of the rates of morbidity in survivors or our estimates of the changes in these rates would be substantially affected.

Over the decade, changes were noted in both infant characteristics and the number of participating centers. Known infant characteristics have been accounted for in the analyses. To evaluate the impact of changes in participating centers, we performed an analysis based on the subset of hospitals that were members throughout the study period, suggesting that the changes in participating hospitals over the course of the study were not responsible for the changes we observed in mortality and morbidity.

We observed a decrease of 3.3% in the rate of severe ROP between 2000 and 2009. It is important to consider that after the report in 2003 from the Early Treatment of Retinopathy of Prematurity Cooperative Group and the subsequent publication of revised guidelines by the American Academy of Pediatrics in 2006, that retinal ablation therapy may have been performed at a less severe stage of ROP. This could have contributed to the reduced incidence of stage 3, 4, or 5 ROP that we observed.[38,39] However, we did not observe a statistically significant increase in the rate of laser or cryosurgery for ROP (data not shown), suggesting that earlier surgical intervention was not the explanation for a decrease in severe ROP. We observed a 0.4% decrease in severe IVH over the decade. Although the overall percentage of infants undergoing any form of cranial imaging did not change significantly over the study period, it is possible that the use of computed tomography and MRI after 2005 for the diagnosis and grading of IVH affected

the detection of IVH. The diagnosis of cystic PVL was made based on cranial ultrasound over the entire study period.

Although our study includes a large and diverse group of North American NICUs, the study sample is not population based. Our findings should only be interpreted as reflecting the outcomes for infants receiving care at North American hospitals with NICUs and should not be generalized to the population of all live born infants of 501 to 1500 g or to those treated in NICUs outside of North America. The study population includes all infants weighing 501 to 1500 g who were born at a participating hospital or transferred to a participating hospital within 28 days of birth. Because this is not a population-based study, these data should be interpreted with caution if used for prenatal counseling.

CONCLUSIONS

Mortality and survival with major neonatal morbidity for infants 501 to 1500 g decreased between 2000 and 2009. Infants weighing 501 to 750 g had the greatest decrease in mortality but the least change in survival with major morbidity. In 2009, nearly half of all infants 501 to 1500 g and 89% of those weighing 501 to 750 g either died or survived after experiencing ≥1 major morbidity during their initial hospital stay, highlighting the continuing challenges facing these vulnerable patients, their families, and the health professionals who care for them.

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Pediatrics originally published online May 21, 2012;