Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993–2012

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Abstract

Importance—Extremely preterm infants contribute disproportionately to neonatal morbidity and mortality.

Objective—To review 20-year trends in maternal/neonatal care, complications, and mortality among extremely preterm infants born at Neonatal Research Network centers.

Design, Setting, Participants—Prospective registry of 34,636 infants 22–28 weeks' gestational age (GA) and 401–1500 gram birthweight born at 26 Network centers, 1993–2012.

Exposure—Extremely preterm birth.

Main Outcomes—Maternal/neonatal care, morbidities, and survival. Major morbidities, reported for infants who survived more than 12 hours, were: severe necrotizing enterocolitis, infection, bronchopulmonary dysplasia, severe intracranial hemorrhage, cystic periventricular leukomalacia, and/or severe retinopathy of prematurity. Regression models assessed yearly changes, adjusting for study center, race/ethnicity, GA, birthweight for GA, and sex.

Results—Use of antenatal corticosteroids increased from 1993 to 2012 (348/1431 [24%] to 1674/1919 [87%], p<0.001), as did cesarean delivery (625/1431 [44%] to 1227/1921 [64%], p<0.001). Delivery room intubation decreased from 1144/1433 (80%) in 1993 to 1253/1922 (65%) in 2012 (p<0.001). After increasing in the 1990s, postnatal steroid use declined to 141/1757 (8%) in 2004 (p<0.001), with no significant change thereafter. Although most infants were ventilated, continuous positive airway pressure without ventilation increased from 120/1666 (7%) in 2002 to 190/1756 (11%) in 2012 (p<0.001). Despite no improvement from 1993 to 2004, rates of late-onset sepsis declined between 2005 and 2012 for infants of each GA (median GA 26 weeks, 109/296 [37%] to 85/320 [27%], adjusted relative risk [aRR]: 0.93 [95% CI, 0.92–0.94]). Rates of other morbidities declined, but bronchopulmonary dysplasia increased between 2009 and 2012 for infants 26–27 weeks (26 weeks, 130/258 [50%] to 164/297 [55%], p<0.001). Survival increased between 2009 and 2012 for infants 23 weeks (41/152 [27%] to 50/150 [33%], aRR: 1.09 [95% CI, 1.05–1.14]) and 24 weeks (156/248 [63%] to 174/269 [65%], aRR: 1.05 [95% CI, 1.03–1.07]), with smaller relative increases for infants 25 and 27 weeks and no change for infants 22, 26 and 28 weeks. Survival without major morbidity increased approximately 2% per year for infants 25–28 weeks with no change for infants 22–24 weeks.

Conclusions and Relevance—Among extremely preterm infants born at US academic centers over the last 20 years, changes in maternal and infant care practices and modest reductions in several morbidities were observed, although bronchopulmonary dysplasia increased. Survival increased most markedly for infants born at 23 and 24 weeks and survival without major morbidity increased for infants 25–28 weeks. These findings may be valuable in counselling families and developing novel interventions.

Introduction

Advances in medicine over the past 2 decades have changed care for mothers in preterm labor and for extremely preterm infants. Slow but steady improvements in outcomes have been reported, with substantial differences across centers.[1–7] Nonetheless, extremely preterm infants continue to contribute disproportionately to the burden of neonatal morbidity, mortality, and long-term neurodevelopmental disability.[8,9] Evaluation of current in-hospital morbidity and mortality data among these smallest and most vulnerable infants is important in counseling families and considering novel interventions to improve outcome.

Since 1987, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) has monitored outcomes and trends in antenatal and postnatal care, morbidities, and mortality among extremely preterm infants born at academic centers of the NRN.[10] The last overview evaluated data from 2003 through 2007.[2] As there have been considerable changes in obstetric and neonatal care over the past 2 decades, this study comprehensively reviews interventions and outcomes of infants 22–28 weeks gestational age (GA) born at NRN hospitals between 1993 and 2012.

Methods

This study evaluated infants born at NRN hospitals between 1993 and 2012, with GA 22 0/7 through 28 6/7 weeks and birthweight (BW) 401–1500 grams. NRN centers are selected by peer review and represent academic institutions with large obstetric and neonatal services, expertise in caring for high-risk mothers and extremely preterm infants, and experience in multicenter clinical research. Study sites are distributed throughout the United States. All delivery hospitals at NRN sites are included in the registry and represent almost 5% of all extremely preterm births in the United States.

From 1993–2007, all very-low-birthweight infants (401–1500 grams) born at or admitted to study centers within 14 days of birth were included in the registry. Eligibility criteria changed in 2008 to include inborn infants with BW 401–1000 grams or GA 22–28 weeks. Our study population of infants 22–28 weeks GA was restricted to inborn infants with BW 401–1500 grams, to maintain consistency over the entire study period.

Data were collected prospectively with maternal pregnancy and delivery information collected soon after birth, and infant data collected until death, hospital discharge/transfer, or 120 days of age. Infants who died in the first 12 hours of life were included in analyses of overall mortality but were excluded from analyses focused on morbidities and respiratory support as these outcomes were not collected for infants who died within 12 hours. Morbidities diagnosed during the initial hospital stay[1,2,10,11–15] were recorded for infants who survived more than 12 hours. Definitions were used consistently over the study period. Detailed respiratory support data were collected beginning 2002.

This study was approved by the institutional review board at each site, with waiver of consent granted at most study sites and written or oral parental consent required by 3 sites.

Outcomes

We focused on changes over time in maternal and neonatal care practices and neonatal morbidity and mortality. Changes in maternal/neonatal characteristics, including maternal age, race/ethnicity (based on chart abstraction using categories specified in the study manual of operations), prenatal care, insulin-dependent diabetes, hypertension; multiple birth; birth defects; infant GA, BW, and small for GA were examined to assess changes over time that might influence outcomes. Care practices reported were chosen because they have been associated with neonatal outcomes and included antenatal steroids, antenatal antibiotics, cesarean delivery, delivery room resuscitation, surfactant therapy, postnatal steroids, and respiratory support. Morbidities included necrotizing enterocolitis, stage 2–3 (NEC)[16,17]; early (72 hours) and late-onset (>72 hours) sepsis, defined by cultures positive for bacteria or fungi, and antibiotic therapy 5 days or intent to treat but death <5 days[18,19]; intracranial hemorrhage (ICH); cystic periventricular leukomalacia (PVL); retinopathy of prematurity (ROP) among infants hospitalized at 28 days; and bronchopulmonary dysplasia (BPD), defined as oxygen use at 36 weeks postmenstrual age or at discharge/transfer if before 36 weeks in infants who survived to 36 weeks. ICH was based on the most severe cranial sonogram prior to hospital discharge, transfer, or death. Grade 3/4 ICH was considered severe.[20] Survival to discharge and survival without major morbidity (NEC, severe ICH, PVL, early or late-onset sepsis or meningitis, BPD or ROP stage 3) were studied.

Statistical Analysis

Descriptive statistics are shown in four 5-year periods (1993–1997, 1998–2002, 2003–2007, 2008–2012) and for the first and last years of the study (1993, 2012), and yearly changes are shown in figures. Analyses examined yearly changes over time, with birth year treated as a continuous variable. Changes in maternal/neonatal characteristics were assessed using linear or logistic models. Linear trends in outcomes were assessed using Poisson regression models with robust variance estimators[21] to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the change per year while adjusting for covariates. Models included covariates for birth year, study center, maternal race/ethnicity, infant GA, SGA, and sex, with exceptions noted in table footnotes. P-values for tests of trends were determined by Score or Wald chi-square or F tests. Analyses were based on infants with non-missing values of covariates and outcomes. Less than 1% of observations were missing values of covariates or outcomes except that approximately 5% of infants could not be evaluated for major morbidity and 4% of infants surviving to 36 weeks postmenstrual age were not evaluated for BPD. Missing values were not imputed with the exception that missing ethnicity for white (0.4%) and black (2%) race was considered to be non-Hispanic.

Graphs of the percent of infants with each outcome by birth year were examined to suggest the modeling strategy with respect to year. Each graph included a local regression (LOESS) curve that was fit using the data proportions and a smoothing parameter (0.3 or 0.4) for assessment of trend. Trends generally consistent over the period were assessed by including year in the models as a single continuous variable. For trends that varied over the period, linear splines with knot points (changes in trend) suggested by the graph were used to assess variation. Where one RR is reported for an outcome, the change per year was estimated for 1993–2012. Where more than one RR is reported, the change per year was estimated for the

periods shown to capture variation in trend over time. Yearly trends in outcomes were assessed overall and for infants of each GA through use of interaction terms between each level of GA and year effects. For outcomes with non-significant year-GA interactions, adjusted RRs from main effects models are reported. For outcomes with significant year-GA interactions, adjusted RRs from models that included the interaction are reported for infants of each GA, with graphs shown by GA in Supplemental Figures.

The primary analyses used data from all centers. Analyses were repeated using data from the centers in the NRN all 20 years. Except as noted, results were similar to those from the primary analyses and are not reported. A 2-sided p-value <0.05 was considered significant. Analyses were completed using SAS statistical software version 9.3 (SAS Institute).

Results

During 1993–2012, 34,636 infants 22–28 weeks GA and 401–1500 grams BW were born at 26 NRN centers. Eight centers participated all 20 years (18,236 infants, 53%), 5 for 14–19 years (26%), 1 for 12 years (4%), 7 for 6–9 years (14%), 1 for 4 years (2%), and 4 for 2 years (2%). Maternal age increased from a mean (SD) of 25.7 (6.5) years in 1993 to 27.8 (6.3) years in 2012, p<0.001 (Table 1). Race/ethnicity changed, with smaller percentages of non-Hispanic black mothers (55% in 1993 to 39% in 2012) and higher percentages of non-Hispanic white and Hispanic mothers (31% to 42% and 12% to 14%, respectively, p<0.001). Maternal hypertension increased from 12% in 1993 to 27% in 2012 (p<0.001) and maternal insulin-dependent diabetes from 2% to 5% (p<0.001).

A major birth defect was reported for 1292 infants (3.7%) and the proportion did not change significantly between 1993 and 2012, p=0.25. The percent of infants from a multiple birth increased from 18% in 1993 to 27% in 1998 (p<0.001), with no further increase noted. Study participants were 52% male, with similar proportions in each year.

Care practices

Use of antenatal corticosteroids increased from 1993 to 1996 (348/1431 [24%] to 1049/1413 [74%], p<0.001; Figure 1). The change varied significantly by GA, with larger relative increases each year among mothers of lower GA infants (22 weeks, 2/79 [3%] to 17/70 [24%], adjusted RR (aRR) [95% CI] for change per year: 1.81 [1.38–2.38]; 28 weeks, 93/310 [30%] to 252/295 [85%], aRR: 1.30 [1.26–1.35]; eFigure 1). After 1996, use increased more slowly; by 2012, 1674/1919 (87%) mothers received at least one dose of corticosteroids (eTable 1). Antenatal antibiotic use increased during the early 1990s from 631/1431 (44%) in 1993 to 1310/1729 (76%) in 1997 (p<0.001; Figure 1, eTable 1). After 1997, antenatal antibiotic use decreased to 1191/1889 (63%) in 2006 (p<0.001) but rose to 1401/1916 (73%) in 2012 (p<0.001). In the 8 centers in the NRN all 20 years, no increase was noted after 2006.

Cesarean section deliveries increased, most markedly from 1993 to 2005 (625/1431 [44%] to 1247/2024 [62%], p<0.001; Figure 1). The increase differed by GA, with larger relative yearly increases among infants of lower GA (eFigure 2, eTable 1). Cesarean deliveries continued to increase slightly after 2005 for infants born at 26 and 27 weeks.

Delivery room tracheal intubation, resuscitation drugs, and chest compression decreased over time, while surfactant use increased (Figure 1, eTable 1). In 1993, 1144/1433 (80%) infants were intubated in the delivery room compared with 1253/1922 (65%) in 2012; decreases differed by GA (eFigure 3). Surfactant was given to 861/1433 (60%) infants in 1993 and 1501/1913 (78%) in 2003, with increases in all GAs except infants born at 22 weeks (eFigure 4). After 2003, surfactant use decreased slightly among infants born at 27–28 weeks.

Among infants who survived more than 12 hours, postnatal corticosteroid use increased significantly in the early 1990s, from 356/1240 (29%) in 1993 to 508/1230 (41%) in 1996 (aRR: 1.18 [1.14–1.21], p<0.001; Figure 1). Postnatal steroid use decreased to a low of 141/1757 (8%) in 2004, p<0.001, with no significant change thereafter.

Respiratory support (2002–2012)

Most infants who survived more than 12 hours were mechanically ventilated (Table 2). In 2002, 1497/1666 (90%) infants received conventional ventilation. Conventional ventilation decreased to 1442/1756 (82%) in 2012; changes per year varied by GA (eTable 2). High frequency ventilation increased from 504/1666 (30%) in 2002 to 646/1569 (41%) in 2007 (aRR: 1.03 [1.01–1.04], p<0.001), with no significant change 2008–2012. The percent never ventilated decreased for infants born at 22–23 weeks, but increased for infants born at 24 and 26–28 weeks (26 weeks, 20/328 [6%] in 2002 to 29/326 [9%] in 2012, aRR: 1.06 [1.02–1.10], p=0.002; 28 weeks, 81/380 [21%] to 128/423 [30%], aRR: 1.05 [1.03–1.07], p<0.001; eTable 2). Nasal synchronized intermittent mandatory ventilation (SIMV) increased from 239/1666 (14%) in 2002 to 657/1755 (37%) in 2012, p<0.001 (Table 2). Nasal SIMV was the highest level of support for 13/1666 (<1%) infants in 2002 but increased to 45/1756 (3%) in 2012, p<0.001. Use of CPAP without ventilation increased from 120/1666 (7%) in 2002 to 190/1756 (11%) in 2012 (aRR: 1.05 [1.03–1.07], p<0.001; eTable 2). Few infants born before 25 weeks received nasal SIMV or CPAP without first receiving mechanical ventilation.

Morbidities

Overall, 689/30789 (2%) infants had early-onset sepsis, with no significant change over the period (eTable 3). In 1993, 89/1240 (7%) infants were diagnosed with NEC, increasing to 187/1496 (13%) in 2008 (p<0.001) before falling to 161/1756 (9%) by 2012 (p<0.01; Figure 2). Among infants surviving more than 3 days, 9482/29252 (32%) were diagnosed with late-onset sepsis, with the percent increasing with decreasing GA (28 weeks: 1396/7149 [20%], 22 weeks: 122/200 [61%]). From 1993 to 2004, the percent of infants with late-onset sepsis remained stable or increased slightly depending on GA (Figure 2, eTable 3). After 2004, the rate of late-onset sepsis decreased for infants of each GA (2005 to 2012, 24 weeks: 143/264 [54%] to 89/225 [40%], aRR: 0.94 [0.93–0.95]; 26 weeks: 109/296 [37%] to 85/320 [27%], aRR: 0.93 [0.92–0.94]; 28 weeks: 84/415 [20%] to 34/418 [8%], aRR: 0.91 [0.90–0.92]; eFigure 5).

The percent of infants with severe ICH decreased from 1993 to 2012 (Figure 2, eTable 3). The reduction was significant for infants born at 26 (44/235 [19%] to 35/321 [11%],

p=0.03), 27 (40/261 [15%] to 25/349 [7%], p=0.02), and 28 weeks (32/297 [11%] to 21/417 [5%], p<0.01) but not for infants 22–25 weeks (eFigure 6). PVL decreased for infants born at 26–28 weeks GA (26 weeks, 15/194 [8%] in 1993 to 13/322 [4%] in 2012, aRR: 0.94 [0.92–0.96]; eTable 3, eFigure 7).

Of the 26,749 infants still hospitalized at 28 days, 24,991 (93%) had an ophthalmologic examination prior to discharge. Retinopathy of prematurity was diagnosed for 15,022/24,987 (60%) overall (3,720/24,951 [15%] with stage 3 or higher), with an inverse relationship between diagnosis and GA (22 weeks: 101/113 [89%], 47/113 [42%] stage 3; 28 weeks: 2156/6289 [34%], 171/6279 [3%] stage 3). Diagnosis of ROP decreased for infants born at 25–28 weeks, with limited or no change for infants born at 22–24 weeks (eTable 3). ROP stage 3 or higher increased from 124/941 (13%) in 1993 to 262/1385 (19%) in 2003, but decreased to 160/1509 (11%) by 2012 (aRR for the change per year 2004–2012: 0.94 [0.93–0.95]; Figure 2).

The diagnosis of BPD rose from 295/911 (32%) in 1993 to 547/1213 (45%) in 2000 (aRR: 1.05 [1.04–1.06]), but decreased to 498/1230 (40%) in 2008 (Figure 2). From 2009–2012, BPD rates increased for infants born at 26 weeks (130/258 [50%] to 164/297 [55%], p<0.001) and 27 weeks (103/312 [33%] to 134/339 [40%], p=0.007), but not for infants 22–25 or 28 weeks (eTable 3, eFigure 8). Among the 8 centers in the NRN all 20 years, BPD rates increased from 2009–2012 for all GAs except 28 weeks.

Survival

Survival increased with increasing GA (2012: 22 weeks, 7/75 [9%]; 28 weeks, 405/430 [94%]; Table 3). Survival rates remained unchanged from 1993 through 2008. After 2008, trends in survival varied by GA (Figure 3). From 2009–2012, survival increased for infants born at 23 weeks (41/152 [27%] to 50/150 [33%], aRR for the change per year: 1.09 [1.05–1.14], p<0.001) and 24 weeks (156/248 [63%] to 174/269 [65%], aRR: 1.05 [1.03–1.07], p<0.001), with smaller relative increases for infants born at 25 weeks (237/300 [79%] to 249/308 [81%], aRR: 1.02 [1.01–1.03]) and 27 weeks (311/345 [90%] to 337/357 [94%], aRR: 1.01 [1.002–1.016]). Survival to discharge did not change significantly between 2009 and 2012 for infants born at 22, 26, and 28 weeks.

Among infants who survived to discharge, survival without major morbidity varied by GA (Table 3, Figure 4), with no significant change in the proportion of infants born at 22–24 weeks who survived to discharge without major morbidity. While 99/1550 (6%) infants born at 22 weeks survived to discharge, only 5 survived without major morbidity. However, an increase of approximately 2% per year was seen for infants born at 25–28 weeks (Figure 4). By 2012, over half of infants born at 28 weeks who survived to discharge survived without major morbidity (1993: 88/207 [43%], 2012: 230/387 [59%], aRR: 1.03 [1.02–1.03], p<0.001). Trends in survival and survival without major morbidity were similar in the 8 centers in the NRN all 20 years (eTable 4).

Survivors remained in hospital an average of 93 days [median (IQR): 85 days (66–109 days)], with median hospitalization varying with GA from 140 days for those born at 22 weeks to 63 days for infants born at 28 weeks. Median postmenstrual age at discharge

decreased from 42 weeks for surviving infants born at 22 weeks GA to 37 weeks for those born at 28 weeks, p<0.001.

Discussion

This study of extremely preterm infants born at NRN centers is the first comprehensive review to our knowledge to evaluate how care practices, major morbidities, and mortality have evolved over a 20-year period. The study provides a global overview and level of detail not presented in earlier studies. Findings demonstrate that progress is being made and outcomes of the most immature infants are improving.

We demonstrated a significant increase in survival to discharge for infants born at 23–25 and 27 weeks, with the largest gains for those born at 23 and 24 weeks. Although methods differed, these findings are consistent with a recent study from the NRN on causes and timing of death among extremely preterm infants.[22] In addition to increasing survival, an important goal of obstetrical and neonatal care is to reduce morbidities and improve neonatal outcome. Perhaps the most important new finding is a significant increase in survival without major neonatal morbidity for infants born at 25–28 weeks. Although overall survival increased for infants 23–24 weeks, few infants less than 25 weeks GA survived without major neonatal morbidity, underscoring the continued need for interventions to improve outcomes for the most immature infants.

At very early GAs, the decision to provide active obstetrical management and neonatal intensive care is complex and requires a team approach with discussions between the obstetrical and neonatal teams and the family.[23–25] All infants in this study were delivered in academic centers with availability of tertiary maternal fetal medicine and comprehensive neonatal care. Changes in race/ethnicity likely reflect changes in the centers in the NRN over time and changes in populations served. About a quarter of infants were multiple births, with a significant increase over the study period, consistent with national trends and increased use of fertility treatments.[26]

An important finding is the increased adherence to care practices that have been associated with improved neonatal outcomes. Antenatal corticosteroids are one of the most effective interventions.[27–31] The 1995 National Institutes of Health consensus statement on antenatal corticosteroids led to widespread use. Recent studies have documented benefits to infants as young as 22–23 weeks. Among our patients, antenatal steroid administration increased from only 24% in 1993 to 87% in 2012. We also found a changing pattern of antenatal antibiotic use and a significant increase in cesarean deliveries between 1993 and 2005, with increases noted for infants of each GA. Increased obstetrical interventions among the most immature infants, 22–24 weeks, suggests increased willingness to provide active management of pregnancies near the limit of viability.

Strategies to reduce lung injury, including less aggressive ventilation, are increasingly embraced. In our cohort, changes in respiratory care were documented with decreased intubation in the delivery room but increased surfactant use, suggesting an increase in selective use of surfactant.[32] Avoidance of intubation in the delivery room might lead to

increased surfactant use if early CPAP is insufficient to prevent alveolar collapse in some infants. There were modest increases in the percent of infants 24–28 weeks who were never ventilated. High frequency ventilation increased for infants at each GA, mainly between 2002 and 2007, and less invasive methods of ventilation (nasal SIMV, CPAP as highest level of support) increased overall. These trends are consistent with changes in care reported by other multicenter networks.[4, 7, 33]

Despite increased use of maternal antibiotics over the years, rates of early-onset sepsis did not change significantly. Earlier NRN studies among extremely preterm infants reported a substantial reduction in early-onset Group B Streptococcal sepsis with a concomitant increase in early-onset *E. coli* sepsis[18, 34]. By contrast, we documented a substantial reduction in late-onset sepsis from 2005 to 2012 for infants of each GA. Although we did not collect information on infection control practices, the reduction in late-onset sepsis likely reflects increased attention to improved hand hygiene, skin care, human milk feeding, uniform practices for catheter insertion and care (central line bundles), and attention to discontinuing invasive devices when not needed.[35–38] Given earlier studies linking infection to increased risk of impairment, decreased rates of late-onset sepsis may contribute to improved long-term outcomes for extremely preterm infants[39]. Rates of ROP decreased for infants born at 25–28 weeks and may be related to changes in oxygen use in the delivery room and oxygen saturation targets or to improved adherence to oxygen targets at NRN hospitals during and since the SUPPORT trial (2005–2009)[40].

Among infants who survived to 36 weeks postmenstrual age, BPD rates increased from 2009–2012 for infants born at 26 and 27 weeks, with significant increases for infants 22–27 weeks born in the 8 centers in the NRN all 20 years. This may partly be explained by increased active resuscitation and intensive care and increased survival, especially for the most immature infants. The effect of decreased intubation/ventilation and decreased postnatal corticosteroid use in our population is unclear, although recent meta-analyses suggest that increased early CPAP with reduced intubation/ventilation has a modest effect in reducing BPD[41], while decreased use of postnatal steroids increases BPD risk[42].

Strengths of this study are the large number of infants and the rigorous prospective data collection. However, the study has several limitations. The NRN cohort is hospital-based rather than population-based. Although large, our cohort is not representative of the entire US preterm population, but rather a selected preterm population from academic centers. Although infants who died within 12 hours were included in the analyses of survival, we collected limited information on these infants and thus could not include them in analyses of morbidities. Although the registry's manual of operations provides detailed definitions, we were unable to evaluate potential diagnostic variabilities across sites (e.g., differences in reading cranial ultrasounds or interpreting ophthalmologic examinations). We presented epidemiologic associations and changes over time, but registry data and the cohort design do not provide definitive reasons for the changes observed.

Although the NRN conducts developmental follow-up on a subset of infants included in the registry, follow-up data are not included in this study. We reported only modest declines in severe ICH and PVL, early markers of brain injury. Given the long-term goal of intact

survival and a healthy neurodevelopmental trajectory, it is critical to develop neuro-protective and neuro-promoting "brain care bundles," similar to infection reduction approaches. Attention to optimal nutrition, limitation of invasive procedures, pain management, infection control practices, and reduction of other inflammatory conditions may also promote healthy neurodevelopment.

Despite improvements in survival, medical science may have reached the limits of what current technologies can provide. On-going studies are addressing whether sequencing the genome can provide useful information beyond current newborn screening to accelerate diagnoses and improve care. Other novel areas that warrant further study include advanced brain imaging to better understand injury, repair and growth; minimally invasive delivery of aerosolized surfactant; tissue engineering and regenerative medicine; and selected growth factors and cellular therapies.

Although survival of extremely preterm infants has increased over the past 2 decades, including survival without major morbidity, the individual and societal burden of preterm birth remains substantial,[43] with approximately 450,000 neonates born prematurely in the United States each year.[44] To truly impact newborn outcomes, a comprehensive and sustained effort to reduce the high rates of preterm birth is necessary.

Conclusions

Among extremely preterm infants born at US academic centers over the last 20 years, changes in maternal and infant care practices and modest reductions in several morbidities were observed, although bronchopulmonary dysplasia increased. Survival increased most markedly for infants born at 23 and 24 weeks and survival without major morbidity increased for infants 25–28 weeks. These findings are valuable in counselling families and developing novel interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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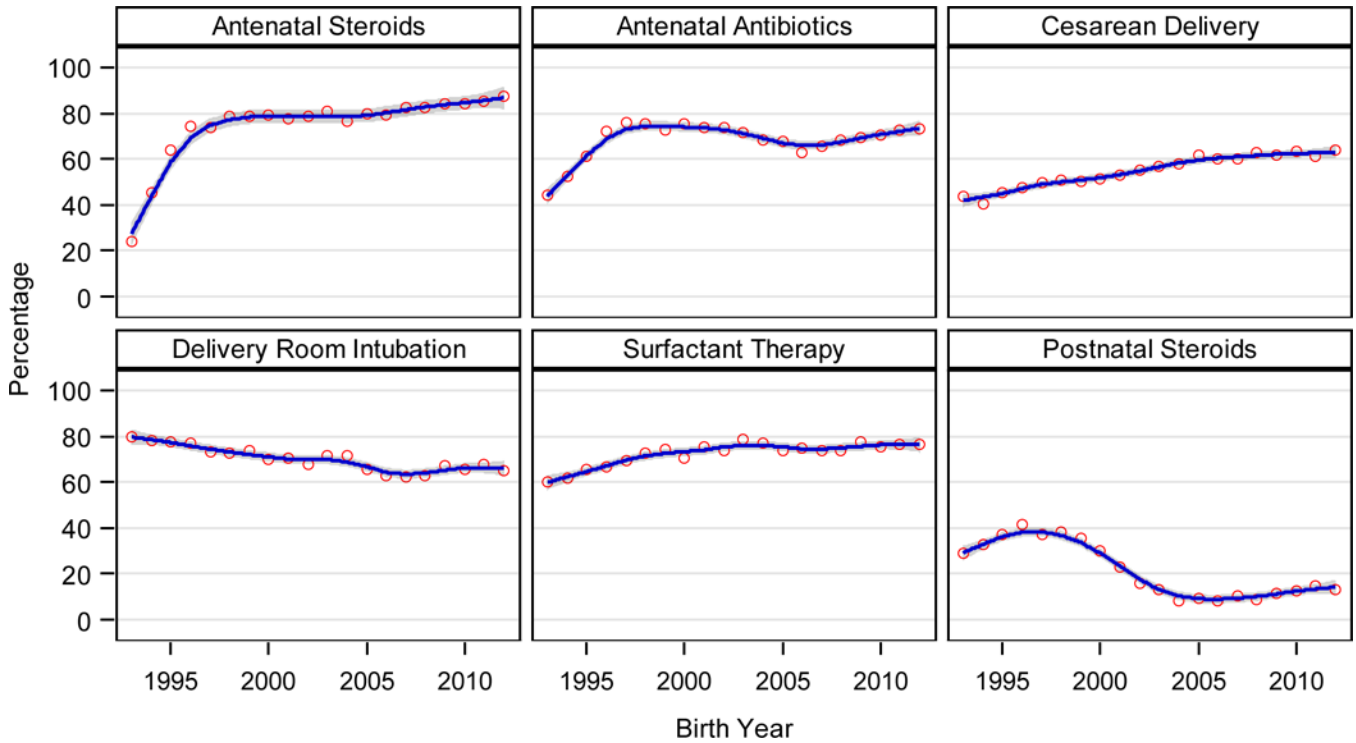
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Figure 1.
Care practices by birth year for infants born at GA 22–28 weeks 1993–2012. In each graph, circles show the percent of infants born each year who received the practice, a smoothed curve shows the trend, and shading indicates a 95% CI for the curve. Shading is not visible where CIs are close to values on the curve. Percents are among all infants, except that for postnatal steroids percents are among infants who survived > 12 hours as this outcome was not collected for infants who died 12 hours of age. Relative risks based on infants of all GA 22–28 weeks are shown for outcomes for which the year-GA interaction was not significant. When the year-GA interaction was significant, graphs and relative risks are shown for each GA in eFigures 1–4. Relative risks for the change per year were adjusted for study center, maternal race/ethnicity, infant GA, SGA, and sex. Total number of infants included [mean (range) per year] in each graph were: antenatal steroids, 34576 [1728 (1214–2022)]; antenatal antibiotics, 34531 [1726 (1210–2020)]; cesarean delivery, 34611 [1730 (1213–2024)]; intubation, 34611 [1730 (1214–2024)]; surfactant, 34599 [1729 (1214–2023)]; postnatal steroids, 30645 [1532 (1036–1802)].

Adjusted RR (95% CI) for the change per year in all infants where year-GA interaction non-significant		
Antenatal Steroids	Antenatal Antibiotics	Cesarean Delivery
(see eFigure 1)	1993–1997: 1.14 (1.12–1.15)	(see eFigure 2)
	1998–2006: 0.978 (0.976–0.981)	
	2007–2012: 1.019 (1.014–1.023)	
Delivery Room Intubation	Surfactant Therapy	Postnatal Steroids
		1993–1996: 1.18 (1.14–1.21)

| (see eFigure 3) | (see eFigure 4) | 1997–2004: 0.82 (0.81–0.83) |
| | | 2005–2012: 1.00 (0.99–1.02) |
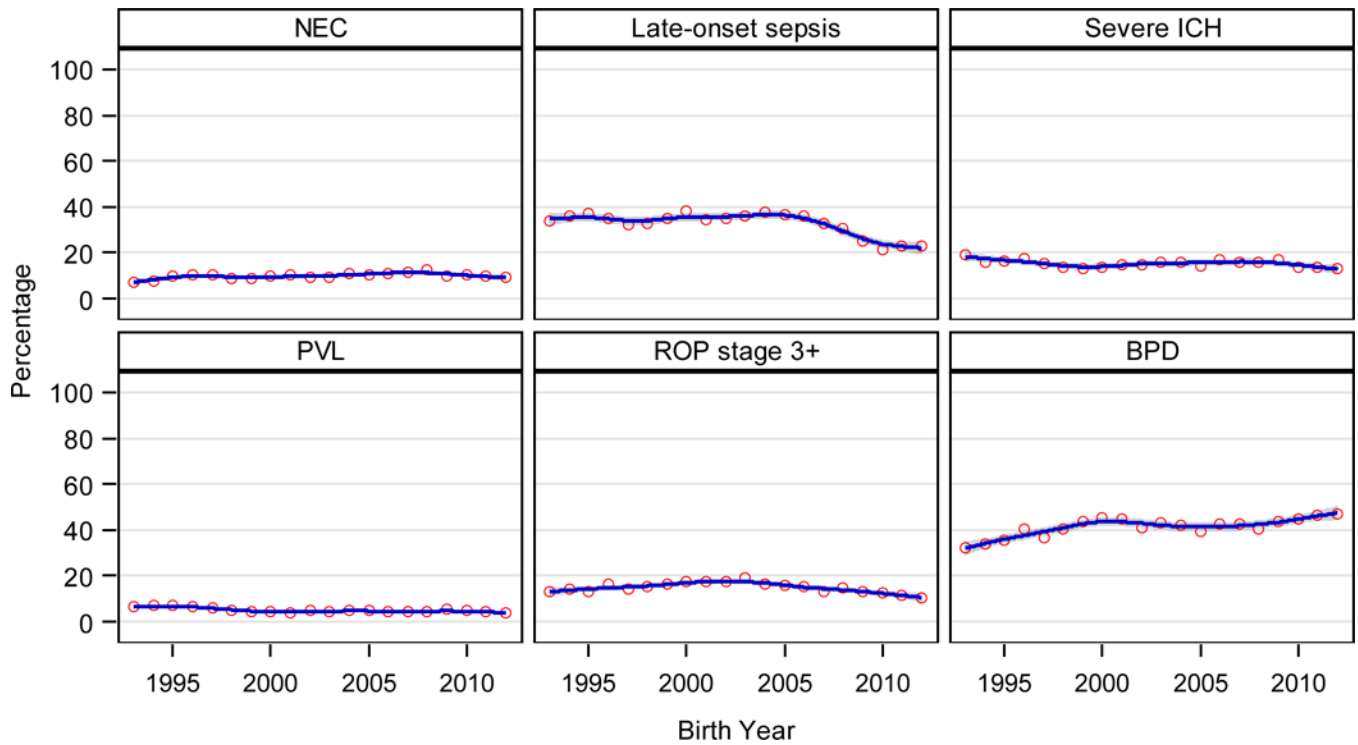
Figure 2.
Neonatal morbidities by birth year for infants born at GA 22–28 weeks 1993–2012. In each graph, circles show the percent of infants born each year diagnosed with the morbidity and a smoothed curve shows the trend. Shading to indicate a 95% CI for each curve is not visible where CIs are close to values on the curve. Percents shown in graphs are among infants of all GA who survived >12 hours with additional restrictions as noted in text and eTable 3. Relative risks based on infants of all GA 22–28 weeks are shown for outcomes for which the year-GA interaction was not significant. When the year-GA interaction was significant, graphs and relative risks are shown for each GA in eFigures 5–8. Relative risks for the change per year were adjusted for study center, maternal race/ethnicity, infant GA, SGA, and sex. Total number of infants included [mean (range) per year] in each graph were: NEC, 30790 [1539 (1035–1809)]; late-onset sepsis, 29252 [1462 (980–1702)]; ICH, 29883 [1494 (1016–1741)]; PVL, 28498 [1424 (769–1744)]; ROP, 24951 [1247 (808–1509)]; BPD, 25000 [1250 (746–1534)].

Adjusted RR (95% CI) for the change per year in all infants where year-GA interaction non-significant		
NEC	Late-onset sepsis	Severe ICH
1993–2008: 1.02 (1.01–1.03) 2009–2012: 0.94 (0.91–0.98)	(see eFigure 5)	(see eFigure 6)
PVL	ROP stage 3+	BPD
(see eFigure 7)	1993–2003: 1.02 (1.01–1.03) 2004–2012: 0.94 (0.93–0.95)	(see eFigure 8)
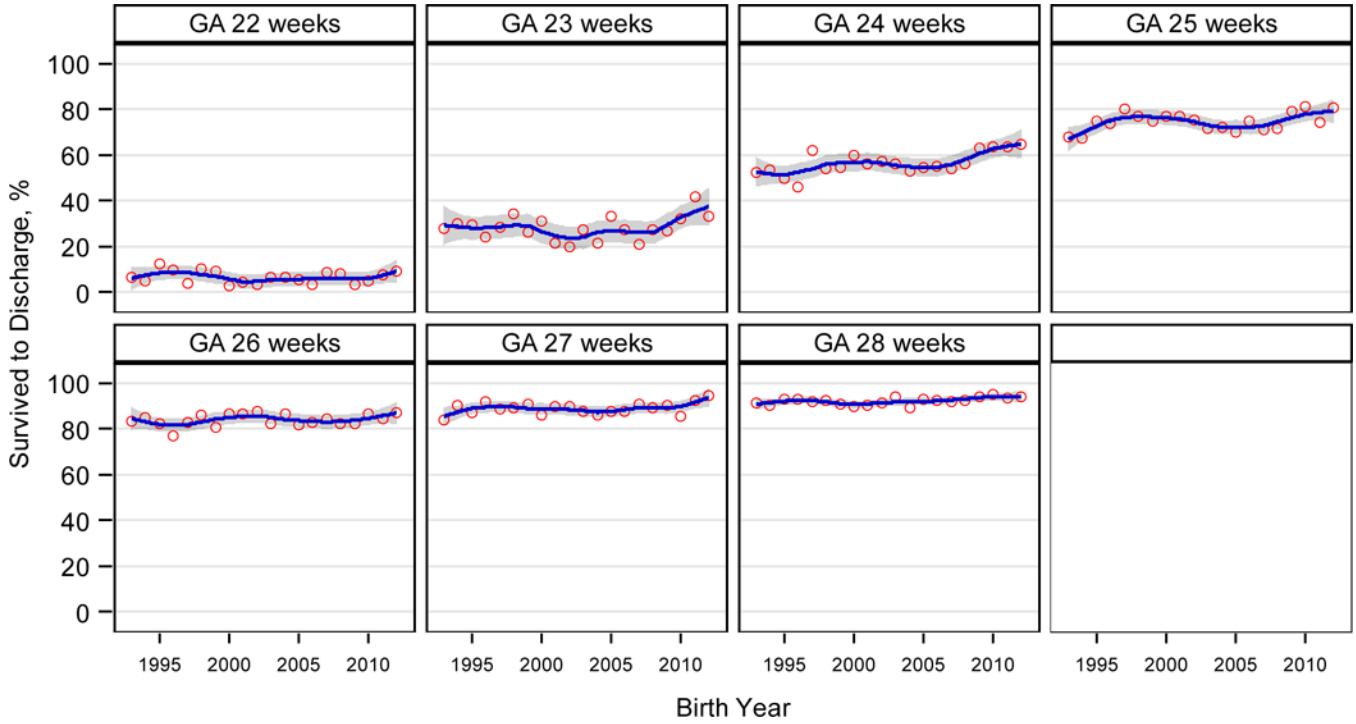
Figure 3.
Survival to discharge by birth year and GA among infants born 1993–2012. In each graph, circles show the percent of infants born each year who survived to discharge, a smoothed curve shows the trend, and shading indicates a 95% CI for the curve. Shading is not visible where CIs are close to values on the curve. Percents are among all infants, including those who died   12 hours. Relative risks for the change per year were adjusted for study center, maternal race/ethnicity, infant GA, SGA, and sex. Survival trends did not vary significantly by GA from 1993–2008 (year-GA interaction, p=0.46) with no significant change in survival (p=0.90) but varied by GA from 2009–2012 (year-GA interaction, p<0.001). Therefore, relative risks are shown for 2009–2012 only. Total number of infants included [mean (range) per year] in each graph were: 22 weeks, 1550 [77 (48–96)]; 23 weeks, 3133 [156 (122–189)]; 24 weeks, 4762 [238 (151–334)]; 25 weeks, 5361 [268 (170–339)]; 26 weeks, 5829 [291 (182–361)]; 27 weeks, 6627 [331(204–399)]; 28 weeks, 7374 [368 (275–430)].

Adjusted RR (95% CI) for the change per year 2009–2012			
22 weeks	23 weeks	24 weeks	25 weeks
1.06 (0.89–1.25)	1.09 (1.05–1.14)	1.05 (1.03–1.07)	1.02 (1.01–1.03)
26 weeks	27 weeks	28 weeks	
1.00 (0.996–1.015)	1.01 (1.002–1.016)	1.00 (0.998–1.011)	
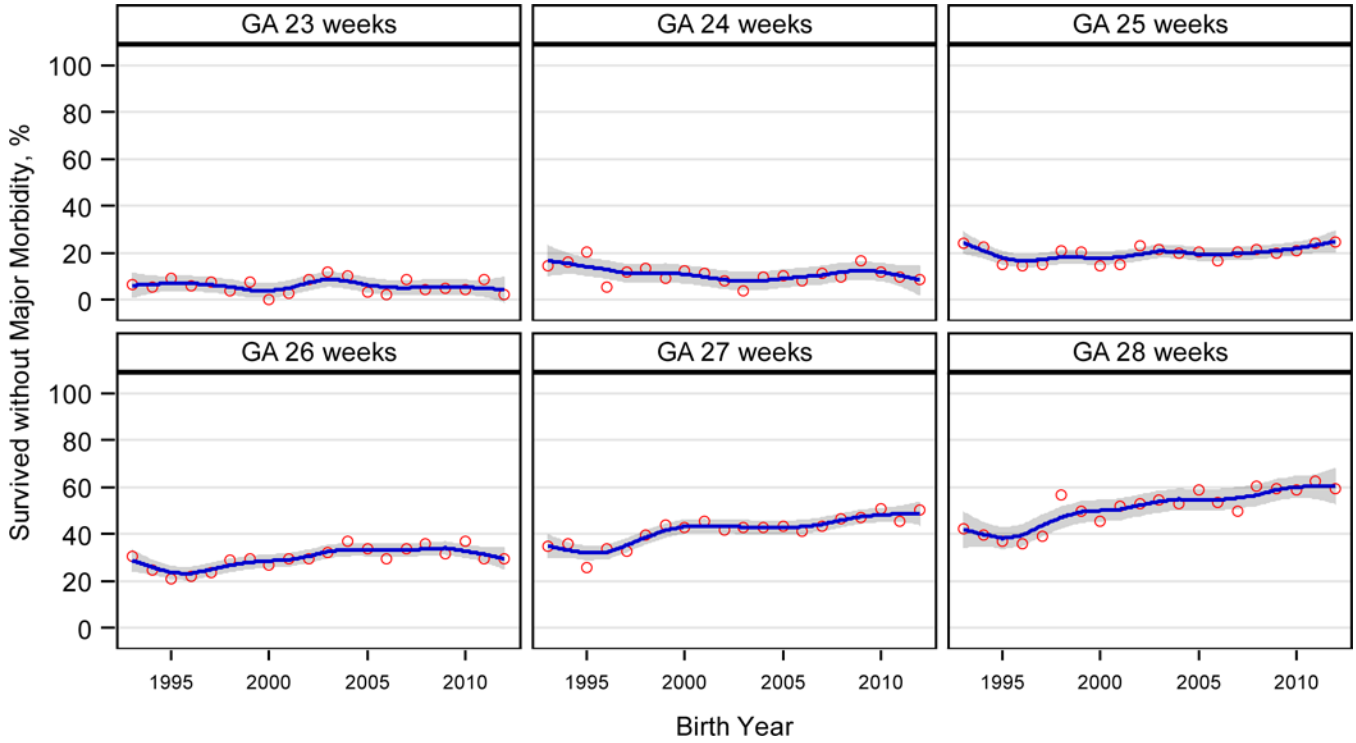
Figure 4.
Survival to discharge without major morbidity among infants who survived to discharge by birth year and GA among infants born 1993–2012. Major morbidity was defined as one or more of necrotizing enterocolitis, infections (early-onset sepsis, late-onset sepsis, or meningitis), BPD, severe ICH, PVL, and ROP stage ≥3. In each graph, circles show the percent of infants who survived without major morbidity each year, a smoothed curve shows the trend, and shading indicates a 95% CI for the curve. Percents are among infants who survived to discharge excluding those not adequately evaluated for major morbidity. Infants born at GA 22 weeks are not shown as only 99 of 1550 survived to discharge and only 5 survived without major morbidity. Relative risks for the change per year were adjusted for study center, maternal race/ethnicity, infant GA, SGA, and sex. Trends varied by GA (year-GA interaction p=0.01). Total number of infants included [mean (range) per year] in each graph were: 23 weeks, 877 [43 (33–69)]; 24 weeks, 2706 [135 (75–183)]; 25 weeks, 4007 [200 (119–249)]; 26 weeks, 4900 [245 (155–313)]; 27 weeks, 5902 [295 (184–350)]; 28 weeks, 6808 [340 (256–405)].

Adjusted RR (95% CI) for the change per year		
23 weeks	24 weeks	25 weeks
1.00 (0.95–1.05)	0.99 (0.97–1.01)	1.02 (1.01–1.03)
26 weeks	27 weeks	28 weeks
1.02 (1.01–1.03)	1.02 (1.02–1.03)	1.03 (1.02–1.03)

Table 1

Maternal and infant characteristics for 34636 infants born at GA 22–28 weeks in NRN centers January 1, 1993 – December 31, 2012

	Total (N=34636)	1993 (N=1433)	2012 (N=1922)	1993–1997 (N=7027)	1998–2002 (N=9132)	2003–2007 (N=9600)	2008–2012 (N=8877)	P-value for linear trend 1993–2012[b]
Maternal characteristics[a]								
Maternal age, y								
Mean (SD)	27.0 (6.6)	25.7 (6.5)	27.8 (6.3)	26.3 (6.7)	26.8 (6.7)	27.2 (6.6)	27.5 (6.4)	<0.001
Race/ethnicity, No. (%)								<0.001
Black, non-Hispanic	14472 (42)	781 (55)	751 (39)	3450 (49)	3908 (43)	3745 (39)	3369 (38)	
White, non-Hispanic	13124 (38)	451 (31)	796 (42)	2483 (35)	3491 (38)	3557 (37)	3593 (41)	
Hispanic	5563 (16)	174 (12)	262 (14)	903 (13)	1425 (16)	1825 (19)	1410 (16)	
Other	1377 (4)	26 (2)	101 (5)	179 (3)	280 (3)	450 (5)	468 (5)	
1 prenatal visit, No. (%)	32235 (93)	1233 (87)	1835 (97)	6296 (90)	8498 (93)	8997 (94)	8444 (96)	<0.001
Insulin-dependent diabetes, No. (%)	1317 (4)	28 (2)	96 (5)	136 (2)	302 (3)	436 (5)	443 (5)	<0.001
Hypertension, No. (%)								
All infants	6991 (20)	172 (12)	508 (27)	1067 (15)	1607 (18)	2121 (22)	2196 (25)	<0.001
By GA, w								
22	94 (6)	2 (3)	6 (8)	13 (4)	19 (4)	34 (8)	28 (8)	
23	242 (8)	2 (2)	25 (17)	21 (3)	49 (6)	84 (10)	88 (11)	
24	596 (13)	10 (6)	49 (18)	67 (8)	122 (10)	198 (14)	209 (17)	
25	1014 (19)	23 (10)	86 (28)	139 (13)	241 (17)	304 (20)	330 (24)	
26	1289 (22)	30 (12)	93 (28)	206 (17)	297 (19)	392 (25)	394 (26)	
27	1684 (25)	49 (17)	116 (33)	282 (21)	374 (22)	498 (27)	530 (31)	
28	2072 (28)	56 (18)	133 (32)	339 (22)	505 (26)	611 (30)	617 (33)	
Infant characteristics								
Multiple birth, No. (%)	8448 (24)	265 (18)	521 (27)	1466 (21)	2265 (25)	2406 (25)	2311 (26)	<0.001
Gestational age, w[c]								

	Total (N=34636)	1993 (N=1433)	2012 (N=1922)	1993–1997 (N=7027)	1998–2002 (N=9132)	2003–2007 (N=9600)	2008–2012 (N=8877)	P-value for linear trend 1993–2012[b]
Mean (SD)	25.7 (1.8)	25.8 (1.8)	25.8 (1.8)	25.7 (1.8)	25.7 (1.8)	25.7 (1.8)	25.8 (1.8)	0.11
Category, No. (%)								
22	1550 (4)	79 (6)	75 (4)	358 (5)	437 (5)	421 (4)	334 (4)	
23	3133 (9)	122 (9)	150 (8)	660 (9)	821 (9)	873 (9)	779 (9)	
24	4762 (14)	163 (11)	269 (14)	871 (12)	1273 (14)	1377 (14)	1241 (14)	
25	5361 (15)	225 (16)	308 (16)	1070 (15)	1397 (15)	1503 (16)	1391 (16)	
26	5829 (17)	250 (17)	333 (17)	1194 (17)	1542 (17)	1580 (16)	1513 (17)	
27	6627 (19)	283 (20)	357 (19)	1337 (19)	1720 (19)	1837 (19)	1733 (20)	
28	7374 (21)	311 (22)	430 (22)	1537 (22)	1942 (21)	2009 (21)	1886 (21)	
BW, g								
Mean (SD)	840 (241)	857 (245)	847 (241)	847 (244)	837 (240)	836 (241)	843 (238)	0.01
Male, No. (%)	18104 (52)	748 (52)	980 (51)	3657 (52)	4743 (52)	5104 (53)	4600 (52)	0.82
Small for GA, No. (%)[d]								
All infants	2497 (7)	90 (6)	135 (7)	445 (6)	674 (7)	722 (8)	656 (7)	0.01
By GA, w								
22	0	0	0	0	0	0	0	
23	95 (3)	2 (2)	9 (6)	15 (2)	23 (3)	32 (4)	25 (3)	
24	275 (6)	5 (3)	14 (5)	36 (4)	72 (6)	86 (6)	81 (7)	
25	401 (7)	15 (7)	23 (8)	68 (6)	109 (8)	116 (8)	108 (8)	
26	492 (8)	21 (8)	34 (10)	93 (8)	140 (9)	130 (8)	129 (9)	
27	554 (8)	20 (7)	25 (7)	102 (8)	137 (8)	178 (10)	137 (8)	
28	680 (9)	27 (9)	30 (7)	131 (9)	193 (10)	180 (9)	176 (9)	
Major birth defect, No. (%)	1292 (4)	50 (3)	87 (5)	342 (5)	283 (3)	336 (4)	331 (4)	0.25

[a]Information was missing as follows: mother's age, 6 infants; prenatal care, 71 infants; maternal diabetes, 66 infants; maternal hypertension, 70 infants; maternal race/ethnicity, 100 infants; gender, 6 infants; small for GA, 6 infants. Infants with black or white maternal race and missing ethnicity were classified as non-Hispanic (2% of blacks, 0.4% of whites). Maternal hypertension was collected as hypertension/pre-eclampsia/eclampsia prior to 2006; beginning 2006 the question was re-worded to ask about hypertension only.

[b]P-values for linear trend across all years were determined by the F or Wald chi-square test from linear or logistic regression models, with adjustment for study center, maternal race/ethnicity, infant gestational age, SGA, and sex except as noted. Models assessing yearly change in maternal race/ethnicity included study center, infant GA, SGA, sex, and year. Models assessing yearly change in GA included study center, maternal race/ethnicity, infant sex, and year. Models assessing yearly change in BW and SGA included study center, maternal race/ethnicity, infant GA, sex, and year. Maternal hypertension, infant GA and small for GA are shown by GA for descriptive purposes only; tests of linear trend were not conducted separately by GA.

[c] Gestational age was assessed using the following hierarchy: (1) by obstetrical measures based on last menstrual period, obstetrical parameters, and/or prenatal ultrasound as recorded in the maternal chart; or (2) by neonatologist's estimate based on physical criteria, neurologic examination, combined physical and gestational age exam (Ballard or Dubowitz), or examination of the lens.

[d] Small for gestational age was defined as birthweight <10th percentile for age and sex based on Alexander percentiles.[9]

Table 2

Respiratory support for 18246 infants born at GA 22–28 weeks in NRN centers January 1, 2002 – December 31, 2012 who survived > 12 hours after birth[a]

No. (%)	2002 (N=1666)	2012 (N=1756)	2003–2007 (N=8546)	2008–2012 (N=8034)
Never used conventional or high-frequency ventilation	167 (10)	255 (15)	886 (10)	1047 (13)
Any high-frequency ventilation	504 (30)	632 (36)	3123 (37)	3070 (38)
Any conventional ventilation	1497 (90)	1442 (82)	7446 (87)	6653 (83)
Any nasal SIMV	239 (14)	657 (37)	1510 (18)	2592 (32)
Any CPAP therapy	1314 (79)	1357 (77)	6680 (78)	6227 (78)
Nasal SIMV highest[b]	13 (<1)	45 (3)	89 (1)	178 (2)
CPAP highest[b]	120 (7)	190 (11)	663 (8)	746 (9)

Information was missing as follows: never used conventional or high-frequency ventilation, 6 infants; high-frequency ventilation, 9 infants; conventional ventilation, 6 infants; any nasal SIMV, 11 infants; any CPAP, 13 infants; nasal SIMV highest, 6 infants; CPAP highest, 6 infants.

[a] Respiratory support outcomes were examined for infants born 2002–2012 due to changes in data collection. Analyses were repeated in the subset of 11 centers in the NRN all years 2002–2012 (N=12,879).

[b] Highest level of support was defined for nasal SIMV as never used conventional or high-frequency ventilation but used nasal SIMV, and for CPAP as never used conventional or high-frequency ventilation or nasal SIMV but received CPAP therapy.

Table 3

Survival to discharge for infants born at GA 22–28 weeks in NRN centers January 1, 1993 – December 31, 2012

No./Total (%)	1993	2012	1993–1997	1998–2002	2003–2007	2008–2012
All infants (N=34636)	**(N=1433)**	**(N=1922)**	**(N=7027)**	**(N=9132)**	**(N=9600)**	**(N=8877)**
Died	426/1433 (30)	409/1922 (21)	1992/7027 (28)	2489/9132 (27)	2725/9600 (28)	2131/8877 (24)
Died within 12 h	193/1433 (13)	166/1922 (9)	909/7027 (13)	1025/9132 (11)	1054/9600 (11)	843/8877 (9)
Survived to discharge						
All infants	1007/1433 (70)	1513/1922 (79)	5035/7027 (72)	6643/9132 (73)	6875/9600 (72)	6746/8877 (76)
22 weeks	5/ 79 (6)	7/ 75 (9)	25/ 358 (7)	27/ 437 (6)	25/ 421 (6)	22/ 334 (7)
23	34/ 122 (28)	50/ 150 (33)	184/ 660 (28)	215/ 821 (26)	226/ 873 (26)	252/ 779 (32)
24	85/ 163 (52)	174/ 269 (65)	465/ 871 (53)	715/1273 (56)	752/1377 (55)	774/1241 (62)
25	153/ 225 (68)	249/ 308 (81)	784/1070 (73)	1065/1397 (76)	1081/1503 (72)	1077/1391 (77)
26	208/ 250 (83)	291/ 333 (87)	980/1194 (82)	1317/1542 (85)	1322/1580 (84)	1281/1513 (85)
27	238/ 283 (84)	337/ 357 (94)	1183/1337 (88)	1536/1720 (89)	1615/1837 (88)	1568/1733 (90)
28	284/ 311 (91)	405/ 430 (94)	1414/1537 (92)	1768/1942 (91)	1854/2009 (92)	1772/1886 (94)
Survival to discharge without major morbidity among all infants[a]						
All infants evaluated[b]	256/1256 (20)	559/1895 (29)	1096/6100 (18)	2119/8869 (24)	2318/9368 (25)	2493/8723 (29)
22 weeks	0/ 79 (0)	0/ 75 (0)	2/ 355 (<1)	3/ 437 (<1)	0/ 421 (0)	0/ 334 (0)
23	2/ 120 (2)	1/ 150 (<1)	12/ 650 (2)	9/ 820 (1)	16/ 871 (2)	13/ 779 (2)
24	12/ 160 (8)	15/ 268 (6)	60/ 850 (7)	77/1269 (6)	65/1377 (5)	87/1238 (7)
25	33/ 208 (16)	61/ 306 (20)	128/1001 (13)	198/1384 (14)	212/1493 (14)	237/1383 (17)
26	52/ 213 (24)	85/ 331 (26)	199/1028 (19)	371/1516 (24)	433/1555 (28)	413/1505 (27)
27	69/ 242 (29)	167/ 353 (47)	305/1090 (28)	628/1650 (38)	669/1785 (37)	735/1693 (43)
28	88/ 234 (38)	230/ 412 (56)	390/1126 (35)	833/1793 (46)	923/1866 (49)	1008/1791 (56)
Infants who survived to discharge (N=25299)	(N=1007)	(N=1513)	(N=5035)	(N=6643)	(N=6875)	(N=6746)
Survival to discharge without major morbidity among infants who survived to discharge						
All survivors evaluated[c]	256/ 830 (31)	559/1486 (38)	1096/4108 (27)	2119/6380 (33)	2318/6643 (35)	2493/6592 (38)
22 weeks	0/ 5 (0)	0/ 7 (0)	2/ 22 (9)	3/ 27 (11)	0/ 25 (0)	0/ 22 (0)
23	2/ 32 (6)	1/ 50 (2)	12/ 174 (7)	9/ 214 (4)	16/ 224 (7)	13/ 252 (5)

No./Total (%)	1993	2012	1993–1997	1998–2002	2003–2007	2008–2012
All infants (N=34636)	**(N=1433)**	**(N=1922)**	**(N=7027)**	**(N=9132)**	**(N=9600)**	**(N=8877)**
24	12/ 82 (15)	15/ 173 (9)	60/ 444 (14)	77/ 711 (11)	65/ 752 (9)	87/ 771 (11)
25	33/ 136 (24)	61/ 247 (25)	128/ 715 (18)	198/1052 (19)	212/1071 (20)	237/1069 (22)
26	52/ 171 (30)	85/ 289 (29)	199/ 814 (24)	371/1291 (29)	433/1297 (33)	413/1273 (32)
27	69/ 197 (35)	167/ 333 (50)	305/ 936 (33)	628/1466 (43)	669/1563 (43)	735/1528 (48)
28	88/ 207 (43)	230/ 387 (59)	390/1003 (39)	833/1619 (51)	923/1711 (54)	1008/1677 (60)

[a] Major morbidity was defined as one or more of necrotizing enterocolitis, infections (early-onset sepsis, late-onset sepsis, or meningitis), BPD, severe ICH, PVL, and ROP stage ≥3.

[b] Of the 34,636 infants in the cohort, 1576 (4.6%) could not be evaluated for survival without major morbidity due to missing information for one or more morbidity. More than half of those missing information were infants born 1993–1997. During this period, BPD and PVL were most frequently missing; PVL was missing when a cranial sonogram was not performed at ≥2 weeks. During 1998–2012, ROP was most frequently missing because no examination was completed prior to discharge. Proportions are among the 33,060 infants who could be evaluated, including infants who died within 12 hours of life.

[c] Proportions are among 23,723 of 25,299 infants who survived to discharge, excluding 1576 infants who survived but could not be evaluated for major morbidity due to missing information.