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Causes and Timing of Death in Extremely Premature Infants from 2000 through 2011

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Abstract

BACKGROUND—Understanding the causes and timing of death in extremely premature infants may guide research efforts and inform the counseling of families.

METHODS—We analyzed prospectively collected data on 6075 deaths among 22,248 live births, with gestational ages of 22 0/7 to 28 6/7 weeks, among infants born in study hospitals within the National Institute of Child Health and Human Development Neonatal Research Network. We compared overall and cause-specific in-hospital mortality across three periods from 2000 through 2011, with adjustment for baseline differences.

RESULTS—The number of deaths per 1000 live births was 275 (95% confidence interval [CI], 264 to 285) from 2000 through 2003 and 285 (95% CI, 275 to 295) from 2004 through 2007; the

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number decreased to 258 (95% CI, 248 to 268) in the 2008–2011 period (P = 0.003 for the comparison across three periods). There were fewer pulmonary-related deaths attributed to the respiratory distress syndrome and bronchopulmonary dysplasia in 2008–2011 than in 2000–2003 and 2004–2007 (68 [95% CI, 63 to 74] vs. 83 [95% CI, 77 to 90] and 84 [95% CI, 78 to 90] per 1000 live births, respectively; P = 0.002). Similarly, in 2008–2011, as compared with 2000–2003, there were decreases in deaths attributed to immaturity (P = 0.05) and deaths complicated by infection (P = 0.04) or central nervous system injury (P<0.001); however, there were increases in deaths attributed to necrotizing enterocolitis (30 [95% CI, 27 to 34] vs. 23 [95% CI, 20 to 27], P = 0.03). Overall, 40.4% of deaths occurred within 12 hours after birth, and 17.3% occurred after 28 days.

CONCLUSIONS—We found that from 2000 through 2011, overall mortality declined among extremely premature infants. Deaths related to pulmonary causes, immaturity, infection, and central nervous system injury decreased, while necrotizing enterocolitis–related deaths increased. (Funded by the National Institutes of Health.)

Although survival among premature infants has improved, prematurity is a leading contributor to neonatal mortality in the United States.[1] Approximately one in four extremely premature infants born at 22 to 28 weeks of gestation does not survive the birth hospitalization; mortality rates decrease with each additional week of completed gestation.[2] Historically, most extremely premature infants died within a few days after birth.[3–5] Among extremely-low-birth-weight infants born at centers in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network between 1993 and 1997, immaturity was the leading cause of death within 12 hours after birth, and pulmonary conditions predominated as the cause of death for those surviving for more than 12 hours.[6] Changes in neonatal care since this period, including changes in prenatal use of glucocorticoids and antibiotic agents, use of surfactants, and ventilation strategies,[7,8] may have led to a relative decrease in deaths attributable to pulmonary causes with a concomitant increase in nonpulmonary causes of death. However, data from a large contemporary cohort of premature infants have not been available to address this question.

We performed the present study to evaluate the causes and timing of death among extremely premature infants in the United States and to assess temporal changes in overall mortality and the causes and timing of death during three periods from 2000 through 2011. We hypothesized that the frequency of pulmonary causes of death, including the respiratory distress syndrome and bronchopulmonary dysplasia, had decreased among extremely premature infants from 2000 through 2011, while the frequency of nonpulmonary causes of death had increased.

METHODS

STUDY POPULATION AND DEFINITIONS

Liveborn infants enrolled in the Generic Database registry of the NICHD Neonatal Research Network were eligible for inclusion in the study if they met the following three criteria: they were born between January 1, 2000, and December 31, 2011, their gestational age at birth was 22 0/7 to 28 6/7 weeks, and they were born in a Neonatal Research Network center. The inclusion criteria were chosen to ensure a consistent selection of infants throughout the study period, because the registry selection criteria were revised in 2008 to exclude infants not born in Neonatal Research Network centers and those with a gestational age at birth of 29 weeks or older. The registry was reviewed and approved by the institutional review board at each participating center. In 3 centers, written or oral informed consent was obtained from the parent or guardian, and in the other 22 centers, a waiver of the requirement for consent was approved by the institutional review board.

Data were collected prospectively by trained research coordinators for all liveborn infants, including those never admitted to an intensive care unit. Gestational age was determined with the use of the best obstetrical estimate based on the date of the last menstrual period, obstetrical variables, prenatal ultrasonography, or all three. If the best obstetrical estimate was unavailable or uncertain, gestational age was determined on the basis of the neonatologist's estimate with the use of physical examination criteria, including the Ballard[9] or Dubowitz[10] examination. Enrolled infants were actively followed from birth to a postnatal age of 120 days, death, hospital discharge, or transfer to another center (whichever occurred first); infants who remained hospitalized for more than 120 days were evaluated for death until 1 year of age. The primary cause of death was prospectively identified and defined as the single underlying, proximate disease that initiated the series of events leading to the final cause of death. The definitions of the specific causes of death are listed in Table S1 in the Supplementary Appendix (available with the full text of this article at NEJM.org) and were included in the manual of operations for the registry. The primary cause of death had to be causally specific to the underlying disease and antecedent to all other causes with respect to time and pathologic relationship. Primary causes of death with infection or central nervous system (CNS) injury as complicating factors were identified from prespecified subcauses. If autopsy findings were available, the cause of death was based on both clinical and autopsy findings. In situations in which the cause of death was not certain, the single cause of death was selected after consultation with the principal investigator (or appointee) from each center. However, interobserver reliability was not assessed. Causes of death that could not be classified as one of the prespecified causes were classified as “other.” Causes that were investigated but could not be established were classified as “unknown.”

STATISTICAL ANALYSIS

We compared the overall and cause-specific mortality rate (number of deaths per 1000 live births) and the proportionate mortality (relative percentage contribution) for the coded causes of death among infants born in three birth-year periods: 2000–2003, 2004–2007, and 2008–2011. We selected comparisons among three birth-year periods instead of individual birth years to provide a sufficiently large sample to control for confounding in our analysis and to provide mortality estimates with greater precision. We compared maternal and neonatal characteristics among the three periods using the Mantel–Haenszel chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables. We performed post hoc subgroup analyses to evaluate potential differences in overall and immaturity-related mortality due to the addition and attrition of centers over time, and we performed sensitivity analyses to evaluate the effects of potential misclassification of deaths due to immaturity, the respiratory distress syndrome, or bronchopulmonary dysplasia (see the Methods section in the Supplementary Appendix). Additional analyses examined causes of death that were complicated by either CNS injury or infection for which another primary cause was listed.

We used the Wald chi-square test in a logistic regression to test the null hypothesis that there was no difference in mortality among the three birth-year periods, after adjusting for potential confounding according to center and important known baseline predictors of death. These variables included gestational age, birth weight, sex, race or ethnic background, multiple gestation (yes vs. no), and small body mass for gestational age (yes vs. no).[11,12] If the overall difference was significant, we performed pairwise birth-period–specific comparisons between 2008–2011 and the two earlier periods. Variables related to clinical therapy, such as prenatal glucocorticoid use or respiratory care, that may have accounted for the changes in mortality over time and were thought to be part of the causal pathway between improvements in care over time and decreases in mortality were not included as covariates in the regression model. To provide protection against model overfitting, the number of parameters in the model for comparison of cause-specific mortality due to CNS injury was reduced because of the small number of events. To avoid an increased type 1 error rate from multiple testing, we provide only descriptive estimates for proportionate mortality; we did not adjust for multiple comparisons of cause-specific mortality. We compared the time to death among the three periods with the Kaplan–Meier method and used the Wilcoxon test, because this test applies more weight to early deaths than does the log-rank test. We considered a two-sided P value of less than 0.05 to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

From January 1, 2000, to December 31, 2011, a total of 22,248 extremely premature infants (22 0/7 to 28 6/7 weeks of gestation) were born alive at one of the 25 study centers and met criteria for inclusion in the study. Among these infants, 6075 (27.3%) died during the birth hospitalization; 6045 (99.5%) of the infants who died had a coded cause of death listed in the registry.

Gestational age, birth weight, and sex were similar across the three birth-year periods for both live births and deaths (Table 1). Extremely premature infants who died were 2 weeks younger in gestational age than surviving infants (mean gestational age at birth, 24.3 vs. 26.3 weeks; $P<0.001$). In addition, the frequency of receipt of prenatal glucocorticoids was lower among mothers whose infants died than among those whose infants survived (62.0% vs. 87.6%, $P<0.01$).

From 2000 through 2011, we detected increases in the percentages of women who received any prenatal care, who received prenatal glucocorticoids, and who delivered by cesarean section, as well as decreases in the percentage of women who received prenatal antibiotic treatment ($P<0.001$ for each comparison among live births across all three periods) (Table 1, and Table S2 in the Supplementary Appendix). The increase in prenatal glucocorticoid administration over the three periods was seen for infants across all gestational ages, including those born at 22 to 23 weeks of gestation. Changes in neonatal characteristics among liveborn infants from 2000–2003 to 2008–2011 included a decrease in the frequency of a temperature below 36°C at admission (from 49.2% to 24.4%, P<0.001), a factor that has previously been associated with increased neonatal mortality,[13] and an increase in the rate of use of high-frequency ventilation (from 28.3% to 38.5%, P<0.001); the rate doubled from 2000–2003 to 2008–2011 for infants born at 22 to 23 weeks of gestation, from 29.3% to 62.4% (Table S2 in the Supplementary Appendix). There was no significant change in the frequency of the use of surfactant therapy from 2000–2003 to 2008–2011 (74.7% to 75.0%, P = 0.63).

TRENDS IN OVERALL MORTALITY

The overall in-hospital mortality rate did not change significantly from 2000–2003 to 2004–2007, but it decreased by 9.6%, from 285 to 258 deaths per 1000 live births, from 2004–2007 to 2008–2011 (adjusted P = 0.003 for the comparison across the three periods) (Table 2). There was a high risk of early death across all three periods, with differences in Kaplan–Meier estimates of survival across the three periods becoming more apparent during the first several postnatal weeks (Fig. S1 and S2 in the Supplementary Appendix). In contrast, the age at death was unchanged over the three periods, occurring at a median of 3 days. Neonatal deaths in the 2000–2011 period were evenly distributed between early deaths (within the first 12 hours of life) and those occurring between 12 hours and 28 days of age (Table 2). In post hoc subgroup analyses, we did not detect significant heterogeneity in the change in overall mortality among the three periods between centers with continuous participation in the Neonatal Research Network and centers with noncontinuous participation (Table S3 in the Supplementary Appendix). Overall, continuous participating centers provided comfort care more frequently in the delivery room (P<0.001) and had higher overall mortality (P<0.001) than did noncontinuous participating centers.

TRENDS IN CAUSE-SPECIFIC MORTALITY

Between 2000 and 2011, deaths were most frequently attributed to immaturity (83 deaths per 1000 live births), the respiratory distress syndrome (64 deaths per 1000 live births), and infection (54 deaths per 1000 live births, attributed to or complicated by infection) (Table 2). Overall, the number of deaths per 1000 live births attributed to the respiratory distress syndrome and bronchopulmonary dysplasia was materially unchanged from 2000–2003 to 2004–2007 (83 and 84 deaths per 1000 live births, respectively) but showed a subsequent decrease in 2008–2011, to 68 deaths per 1000 live births (adjusted P = 0.002 for the comparison across the three periods). The decrease in deaths attributed to pulmonary causes accounted for 53% of the overall reduction in mortality from 2000–2003 to 2008–2011. In contrast, increases in deaths attributed to necrotizing enterocolitis offset the overall reduction in mortality by 26%. In addition, changes over time in the frequencies of deaths attributed to immaturity were not significant in a sensitivity analysis limited to infants born before 24 weeks of gestation (Table S4 in the Supplementary Appendix). Only 3% of deaths coded as “other” had a specification of the cause of death. We reviewed the records of these patients and found that the frequency of coexisting conditions in infants with deaths coded as “other” was similar to that among infants with a specific coded cause of death (Table S5 in the Supplementary Appendix).

CAUSE OF DEATH ACCORDING TO POSTNATAL AGE

From 2000 through 2011, deaths among infants who died within 12 hours after birth were most commonly attributed to immaturity (Fig. 1, and Table S6 in the Supplementary Appendix). For infants surviving longer than 12 hours, deaths were most commonly attributed to the respiratory distress syndrome; this condition was considered to underlie 49.5% of deaths in the first 14 days and 42.8% of deaths in the first month of life. From 15 to 60 postnatal days, necrotizing enterocolitis was the most common cause of death; after 60 days, bronchopulmonary dysplasia became the predominant cause of death. We identified some potential misclassification between deaths due to the respiratory distress syndrome and deaths due to bronchopulmonary dysplasia (e.g., deaths attributed to bronchopulmonary dysplasia within the first 28 postnatal days or to the respiratory distress syndrome after 28 postnatal days); however, the overall results of a sensitivity analysis to account for this misclassification were consistent with those of the primary analysis (Table S4 in the Supplementary Appendix). In addition, the percentage of deaths attributed to infection increased substantially from the first postnatal week (3.5% of all deaths) to the second postnatal week (15.3% of all deaths).

CAUSE AND TIMING OF DEATH ACCORDING TO GESTATIONAL AGE

Immaturity was most commonly identified as the cause of death for infants born at 22 or 23 weeks of gestation; most of these infants died within 12 hours after birth and were not intubated in the delivery room (Table 3, and Table S7 in the Supplementary Appendix). In contrast, deaths among infants born at 24 to 27 weeks of gestation were primarily attributed to the respiratory distress syndrome; the majority of deaths among these infants occurred from 12 hours to 28 days of age, but more than 20% of deaths occurred after 28 days of age (Table 4). As gestational age increased, the percentage of deaths attributed to necrotizing enterocolitis and congenital anomalies also increased. The largest absolute declines in mortality from 2000–2003 to 2008–2011 were observed for infants born at 23 or 24 weeks of gestation (Table 4).

DISCUSSION

This study shows a reduction in death rates among extremely premature infants born at NICHD Neonatal Research Network centers between 2000 and 2011. The decline in overall mortality was greatest between 2004–2007 and 2008–2011, a period during which the relative decrease in the overall mortality rate was 9.6%. More than half the decrease in overall mortality was accounted for by a reduction in deaths attributed to the respiratory distress syndrome and bronchopulmonary dysplasia. In contrast, deaths attributed to necrotizing enterocolitis increased significantly from 2000–2003 to 2008–2011. The trends we observed in deaths attributed to pulmonary causes or necrotizing enterocolitis are consistent with trends from 1988 through 2008 in infants born before 31 weeks of gestation, as reported in the U.K. Perinatal Mortality Survey.[14] However, we found a decrease in deaths attributed to or complicated by infection, whereas increases in infection-related deaths were reported in the U.K. Perinatal Mortality Survey. The increase in mortality attributed to necrotizing enterocolitis may be related to improvements in the early survival of infants who would have otherwise died before they reached the typical postnatal age at which necrotizing enterocolitis occurs. Data from the U.K. Perinatal Mortality Survey and a Swedish cohort[15] are consistent with these observations.

Improved overall survival of premature infants has recently been reported by researchers from the Vermont Oxford Network,[16] the Canadian Neonatal Network,[17] and Japan,[18] although these studies did not evaluate changes in cause-specific mortality associated with reductions in overall mortality. The observed decline in overall mortality in our study is unlikely to be a result of more aggressive resuscitation in the delivery room for infants at the margins of viability, because the frequency of aggressive resuscitation in the delivery room, including endotracheal intubation for infants born before 24 weeks of gestation, was similar across the three periods. However, increases in the use of high-frequency ventilation may reflect more aggressive respiratory care over time for the most immature infants in the neonatal intensive care unit.

The limitations of our study should be acknowledged. Determining a single cause of death when multiple causes may play a role can be difficult and subjective. We used prospective evaluation with standardized definitions and inclusion of autopsy findings, when available, in an effort to minimize bias in determining the primary cause of death, but the validity of such determinations is uncertain. Misclassification may have occurred, particularly in attributing causes of death to immaturity versus the respiratory distress syndrome or bronchopulmonary dysplasia. To address this, we evaluated the sensitivity of our findings to potential misclassification of these causes and also characterized “pulmonary” deaths attributed to either the respiratory distress syndrome or bronchopulmonary dysplasia. We also combined deaths that were coded as either directly attributed to or complicated by infection or CNS injury, because the distinction between causation and co-occurrence is often unclear. We could not identify a cause of death for the 13.7% of infants whose cause of death was classified as “other,” despite attempts to further characterize this group of infants. Also, we could not determine the frequency of withdrawal or limitation of intensive care and its effect on changes in mortality. In addition, we did not adjust for multiple comparisons of cause-specific mortality, which increased the likelihood that some significant differences in cause-specific mortality over time may have been the result of chance. Finally, Neonatal Research Network centers may not be representative of other tertiary, large neonatal intensive care units, and this may limit the generalizability of our findings.

In conclusion, from 2000 through 2011, rates of death overall — and specifically, deaths attributed to immaturity or pulmonary causes (bronchopulmonary dysplasia and the respiratory distress syndrome) and those attributed to or complicated by infection or CNS injury — decreased among extremely premature infants, while deaths attributed to necrotizing enterocolitis increased. Our findings underscore the continued need to develop and implement strategies for reducing the potentially lethal complications of premature birth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mathews, TJ.; MacDorman, MF. Infant mortality statistics from the 2009 period linked birth/infant death data set. Hyattsville, MD: National Centers for Health Statistics; 2013. (http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_08.pdf)
2. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010; 126:443–56. [PubMed: 20732945]
3. 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):E1. [PubMed: 11134465]
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):E37. [PubMed: 10699139]
5. Mohamed MA, Nada A, Aly H. Day-by-day postnatal survival in very low birth weight infants. Pediatrics. 2010; 126(2):e360–e366. [PubMed: 20624810]
6. Shankaran S, Fanaroff AA, Wright LL, et al. Risk factors for early death among extremely low-birth-weight infants. Am J Obstet Gynecol. 2002; 186:796–802. [PubMed: 11967510]
7. Hintz SR, Poole WK, Wright LL, et al. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. Arch Dis Child Fetal Neonatal Ed. 2005; 90:F128–F133. [PubMed: 15724036]
8. Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol. 2007; 196(2):147.e1–8. [PubMed: 17306659]
9. Ballard JL, Novak KK, Driver M. A simplified score for assessment of fetal maturation of newly born infants. J Pediatr. 1979; 95:769–74. [PubMed: 490248]
10. Dubowitz LM, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. J Pediatr. 1970; 77:1–10. [PubMed: 5430794]
11. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity — moving beyond gestational age. N Engl J Med. 2008; 358:1672–81. [PubMed: 18420500]
12. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. Am J Obstet Gynecol. 2000; 182:198–206. [PubMed: 10649179]
13. Laptook AR, Salhab W, Bhaskar B. Admission temperature of low birth weight infants: predictors and associated morbidities. Pediatrics. 2007; 119(3):e643–e649. [PubMed: 17296783]
14. Berrington JE, Hearn RI, Bythell M, Wright C, Embleton ND. Deaths in preterm infants: changing pathology over 2 decades. J Pediatr. 2012; 160:49–53. [PubMed: 21868028]
15. Ahle M, Drott P, Andersson RE. Epidemiology and trends of necrotizing enterocolitis in Sweden: 1987–2009. Pediatrics. 2013; 132(2):e443–e451. [PubMed: 23821702]
16. Horbar JD, Carpenter JH, Badger GJ, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics. 2012; 129:1019–26. [PubMed: 22614775]

17. Shah PS, Sankaran K, Aziz K, et al. Outcomes of preterm infants <29 weeks gestation over 10-year period in Canada: a cause for concern? J Perinatol. 2012; 32:132–8. [PubMed: 21593814]

18. Kusuda S, Fujimura M, Uchiyama A, Totsu S, Matsunami K. Trends in morbidity and mortality among very-low-birth-weight infants from 2003 to 2008 in Japan. Pediatr Res. 2012; 72:531–8. [PubMed: 22922774]

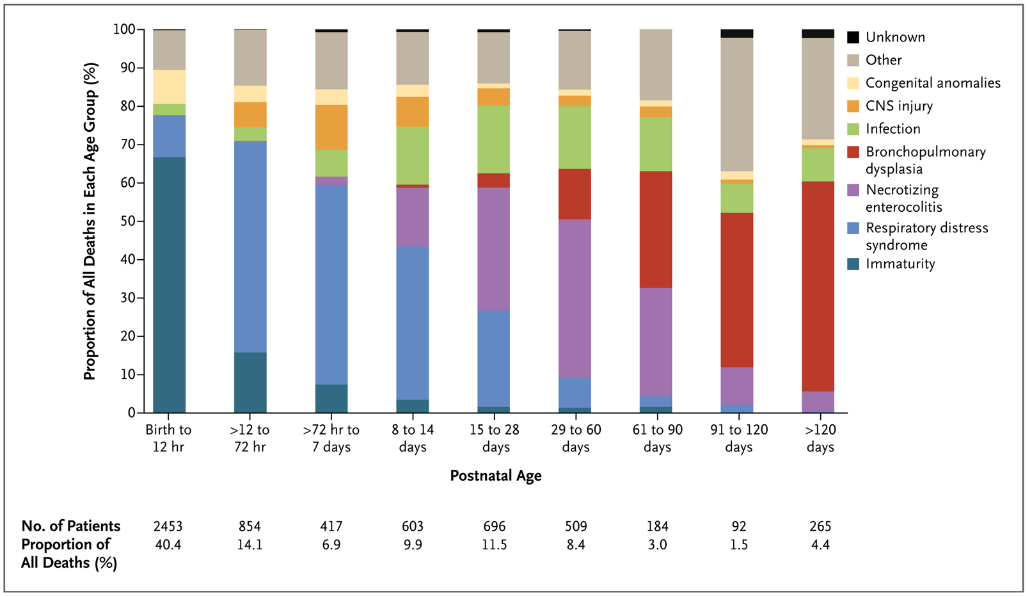

Figure 1. Proportionate Mortality for Major Causes of Death, According to Postnatal Age

CNS denotes central nervous system.

Table 1

Characteristics of the Cohort.*

Characteristic	Live Births			Deaths		
	2000–2003 (N = 7440)	2004–2007 (N = 7684)	2008–2011 (N = 7124)	2000–2003 (N = 2043)	2004–2007 (N = 2193)	2008–2011 (N = 1839)
Gestational age — wk	25.7±1.8	25.7±1.8	25.7±1.8	24.3±1.8	24.3±1.7	24.3±1.7
Birth weight — g†	837±241	834±240	839±253	660±192	661±192	658±230
Female sex — no./total no. (%)	3506/7440 (47.1)	3638/7682 (47.4)	3420/7123 (48.0)	889/2043 (43.5)	948/2192 (43.2)	790/1839 (43.0)
Multiple gestation — no. (%)	1826 (24.5)	1923 (25.0)	1837 (25.8)	521 (25.5)	582 (26.5)	499 (27.1)
Maternal race — no./total no. (%)‡§¶						
Black	3139/7433 (42.2)	3054/7603 (40.2)	2741/6983 (39.3)	903/2037 (44.3)	889/2163 (41.1)	704/1797 (39.2)
White	3997/7433 (53.8)	4194/7603 (55.2)	3818/6983 (54.7)	1063/2037 (52.2)	1160/2163 (53.6)	983/1797 (54.7)
Other	297/7433 (4.0)	355/7603 (4.7)	424/6983 (6.1)	71/2037 (3.5)	114/2163 (5.3)	110/1797 (6.1)
Mother of Hispanic origin — no./total no. (%)¶	1258/7136 (17.6)	1498/7389 (20.3)	1183/6852 (17.3)	363/1966 (18.5)	446/2086 (21.4)	334/1750 (19.1)
Mother received prenatal glucocorticoids — no./total no. (%)‡‖	5882/7432 (79.1)	6071/7658 (79.3)	5942/7108 (83.6)	1252/2040 (61.4)	1314/2191 (60.0)	1193/1832 (65.1)
Born by cesarean delivery — no./total no. (%)‡§	4023/7429 (54.2)	4595/7681 (59.8)	4404/7119 (61.9)	834/2039 (40.9)	1010/2191 (46.1)	854/1834 (46.6)
Small for gestational age — no./total no. (%)§**	553/7440 (7.4)	590/7682 (7.7)	623/7120 (8.8)	215/2043 (10.5)	263/2192 (12.0)	284/1836 (15.5)
Intubated in delivery room — no./total no. (%)‡††	5198/7433 (69.9)	5048/7679 (65.7)	4657/7121 (65.4)	1372/2039 (67.3)	1416/2188 (64.7)	1157/1838 (62.9)
Underwent chest compressions in delivery room — no./total no. (%)	694/7432 (9.3)	580/7677 (7.6)	610/7122 (8.6)	307/2040 (15.0)	267/2186 (12.2)	250/1839 (13.6)
Received comfort care in delivery room — no./total no. (%)‡‡	527/7433 (7.1)	571/7679 (7.4)	520/7121 (7.3)	527/2039 (25.8)	571/2188 (26.1)	520/1838 (28.3)
5-min Apgar score — median (IQR)‡§ §§	7 (5–8)	7 (5–8)	7 (5–8)	4 (1–7)	5 (1–7)	4 (1–7)
Temperature at admission <36.0°C — no./total no. (%)‡§¶¶	1691/3439 (49.2)	2870/6765 (42.4)	1476/6051 (24.4)	434/697 (62.3)	832/1424 (58.4)	393/1096 (35.9)
Underwent surfactant therapy — no./total no. (%)	5537/7413 (74.7)	5751/7679 (74.9)	5341/7118 (75.0)	1319/2042 (64.6)	1432/2190 (65.4)	1145/1839 (62.3)

Characteristic	Live Births			Deaths		
	2000–2003 (N = 7440)	2004–2007 (N = 7684)	2008–2011 (N = 7124)	2000–2003 (N = 2043)	2004–2007 (N = 2193)	2008–2011 (N = 1839)
Underwent high-frequency ventilation for ≥1 day — no./total no. (%)[‡§]	2104/7439 (28.3)	2593/7421 (34.9)	2502/6502 (38.5)	943/2043 (46.2)	1064/1932 (55.1)	857/1228 (69.8)

[*] Plus–minus values are means ±SD. IQR denotes interquartile range.

[†] Data for birth weight were missing for 3 live births in the 2008–2011 period; all 3 of the infants died.

[‡] P<0.001 by the Mantel–Haenszel chi-square test (categorical variables) or the Kruskal–Wallis test (continuous variables) for the comparison of live births among the three periods.

[§] P<0.001 for the comparison of deaths among the three periods.

[¶] Maternal race and ethnic background were self-selected by the mother from options defined by federally funded study guidelines. The category “other” included American Indian, Alaskan Native, Asian, Pacific Islander (including Native Hawaiian), more than one race, and other or not specified.

[||] P = 0.02 for the comparison of deaths among the three periods.

[**] P = 0.003 for the comparison of live births among the three periods.

[††] P = 0.005 for the comparison of deaths among the three periods.

[‡‡] Comfort care in the delivery room was defined as no endotracheal intubation and death within 12 hours after birth.

[§§] Data for the 5-minute Apgar score were missing for 173 infants: 51 live births and 39 deaths in 2000–2003, 62 live births and 56 deaths in 2004–2007, and 60 live births and 55 deaths in 2008–2011.

[¶¶] Data for temperature at admission were not collected in 2000 or 2001.

Table 2

Overall Causes of Death among Extremely Premature Infants, 2000–2011.*

Variable	2000–2003	2004–2007	2008–2011	All Years	P Value
Total live births	7440	7684	7124	22,248	
Total deaths	2043	2193	1839	6075	
Overall mortality rate per 1000 live births (95% CI)†	275 (264–285)‡	285 (275–295)‡	258 (248–268)	273 (267–279)	0.003
Cause-specific mortality rate per 1000 live births (95% CI)†§					
Congenital anomalies	16 (13–19)	14 (12–17)	13 (10–16)	14 (13–16)	0.31
Respiratory distress syndrome	65 (60–71)‡	69 (63–75)‡	56 (51–62)	64 (60–67)	0.02
Bronchopulmonary dysplasia	18 (15–21)	15 (13–18)	12 (10–15)	15 (13–17)	0.09
Pulmonary: respiratory distress syndrome plus bronchopulmonary dysplasia	83 (77–90)‡	84 (78–90)‡	68 (63–74)	79 (75–82)	0.002
Infection	22 (19–25)	24 (21–28)	19 (16–22)	22 (20–24)	0.20
Necrotizing enterocolitis	23 (20–27)‡	29 (25–33)	30 (27–34)	28 (25–30)	0.04
CNS injury¶	7 (5–9)	11 (9–14)	10 (8–13)	9 (8–11)	0.21
Immaturity	86 (80–93)‡	81 (75–88)	81 (75–88)	83 (79–87)	0.04
Other	37 (33–42)	40 (36–45)	34 (30–39)	37 (35–40)	0.20
Deaths complicated or caused by infection — no. per 1000 live births (95% CI)†	55 (50–61)	62 (57–68)‡	45 (41–50)	54 (51–58)	0.001
Complicated by infection‖	33 (30–38)‡	38 (34–42)‡	26 (23–30)	33 (30–35)	0.004
Caused by infection**	22 (19–25)	24 (21–28)	19 (16–22)	22 (20–24)	0.20
Deaths complicated or caused by CNS injury — no. per 1000 live births (95% CI)†	31 (27–35)‡	28 (25–32)	24 (20–28)	28 (25–30)	0.003
Complicated by CNS injury††	24 (21–28)‡	17 (14–20)	13 (11–16)	18 (17–20)	<0.001
Caused by CNS injury‡‡	7 (5–9)	11 (9–14)	10 (8–13)	9 (8–11)	0.21
Postnatal age at death in days — median (IQR)	3 (1–17)	3 (1–20)	3 (1–17)	3 (1–18)	>0.99
Time of death — no./total no. (%)					0.72
0 to 12 hr	837/2043 (41.0)	845/2192 (38.5)	771/1838 (41.9)	2453/6073 (40.4)	
>12 hr to 28 days	867/2043 (42.4)	940/2192 (42.9)	763/1838 (41.5)	2570/6073 (42.3)	
>28 days	339/2043 (16.6)	407/2192 (18.6)	304/1838 (16.5)	1050/6073 (17.3)	

Variable	2000–2003	2004–2007	2008–2011	All Years	P Value
Autopsy performed — no./total no. (%)	460/1960 (23.5)	489/2077 (23.5)	331/1746 (19.0)	1280/5783 (22.1)	0.001

[*] CI denotes confidence interval, and CNS central nervous system.

[†] Comparisons were adjusted for center, gestational age, birth weight, sex, race, multiple gestation (yes vs. no), and whether small for gestational age (yes vs. no). A total of 288 patients (1.3%) with missing data for variables in the regression model were excluded. For cause-specific mortality estimates, all live births were considered at risk. Unadjusted confidence intervals were obtained with the use of the exact (Clopper–Pearson) method. Reported P values indicate the results of a test for differences in mortality among all three periods. Relative changes in mortality and P values from pairwise comparisons among the three periods are provided in Table S8 in the Supplementary Appendix.

[‡] P<0.05 for pairwise adjusted comparisons with the 2008–2011 period.

[§] Thirty deaths coded as having an unknown cause are not included.

[¶] Centers added in 2011 were combined for center-adjusted comparisons of CNS injury because of the small number of events.

[||] This category includes the following subcauses: respiratory distress syndrome with infection, bronchopulmonary dysplasia with infection, necrotizing enterocolitis with sepsis, and severe intraventricular hemorrhage with sepsis.

[**] This category includes the following subcauses: suspected sepsis and proven sepsis.

[††] This category includes the following subcauses: respiratory distress syndrome with severe intraventricular hemorrhage and bronchopulmonary dysplasia with CNS injury.

[‡‡] This category includes the following subcauses: severe intraventricular hemorrhage and severe intraventricular hemorrhage with sepsis.

Table 3

Cause of Death According to Gestational Age.

Cause of Death	22 Wk	23 Wk	24 Wk	25 Wk	26 Wk	27 Wk	28 Wk
				number of infants (percent)			
All infants (N = 6075)							
Total deaths*	931 (15.3)	1483 (24.4)	1338 (22.0)	888 (14.6)	582 (9.6)	492 (8.1)	361 (5.9)
Cause							
Congenital anomalies	31 (3.3)	38 (2.6)	41 (3.1)	30 (3.4)	47 (8.1)	58 (11.8)	72 (19.9)
Respiratory distress syndrome	34 (3.7)	337 (22.7)	450 (33.6)	298 (33.6)	142 (24.4)	106 (21.5)	50 (13.9)
Bronchopulmonary dysplasia	3 (0.3)	40 (2.7)	100 (7.5)	76 (8.6)	59 (10.1)	34 (6.9)	24 (6.6)
Infection	22 (2.4)	79 (5.3)	126 (9.4)	94 (10.6)	70 (12.0)	61 (12.4)	31 (8.6)
Necrotizing enterocolitis	5 (0.5)	67 (4.5)	136 (10.2)	122 (13.7)	101 (17.4)	102 (20.7)	79 (21.9)
CNS injury	3 (0.3)	38 (2.6)	73 (5.5)	42 (4.7)	26 (4.5)	18 (3.7)	6 (1.7)
Immaturity	797 (85.6)	778 (52.5)	188 (14.1)	49 (5.5)	22 (3.8)	8 (1.6)	2 (0.6)
Other	36 (3.9)	101 (6.8)	219 (16.4)	168 (18.9)	114 (19.6)	100 (20.3)	92 (25.5)
Unknown	0	5 (0.3)	5 (0.4)	9 (1.0)	1 (0.2)	5 (1.0)	5 (1.4)
Infants surviving >12 hr (N = 3620)							
Total deaths†	97 (2.7)	650 (18.0)	986 (27.2)	729 (20.1)	471 (13.0)	410 (11.3)	277 (7.7)
Cause							
Congenital anomalies	0	2 (0.3)	8 (0.8)	16 (2.2)	14 (3.0)	26 (6.3)	33 (11.9)
Respiratory distress syndrome	28 (28.9)	271 (41.7)	360 (36.5)	242 (33.2)	119 (25.3)	92 (22.4)	37 (13.4)
Bronchopulmonary dysplasia	3 (3.1)	40 (6.2)	100 (10.1)	76 (10.4)	59 (12.5)	34 (8.3)	24 (8.7)
Infection	12 (12.4)	65 (10.0)	112 (11.4)	78 (10.7)	64 (13.6)	53 (12.9)	28 (10.1)
Necrotizing enterocolitis	5 (5.2)	67 (10.3)	136 (13.8)	122 (16.7)	101 (21.4)	102 (24.9)	79 (28.5)
CNS injury	3 (3.1)	38 (5.8)	73 (7.4)	42 (5.8)	26 (5.5)	17 (4.1)	6 (2.2)
Immaturity	36 (37.1)	96 (14.8)	46 (4.7)	20 (2.7)	6 (1.3)	4 (1.0)	0
Other	10 (10.3)	66 (10.2)	147 (14.9)	126 (17.3)	82 (17.4)	79 (19.3)	66 (23.8)
Unknown	0	5 (0.8)	4 (0.4)	7 (1.0)	0	3 (0.7)	4 (1.4)

*Percentages in this row are percentages of all deaths.

†Percentages in this row are percentages of all deaths after 12 hr.

Table 4

Overall Mortality and Timing of Death According to Gestational Age.

Variable	22 Wk	23 Wk	24 Wk	25 Wk	26 Wk	27 Wk	28 Wk
Mortality rate per 1000 live births (95% CI)							
All years	949 (933–961)	730 (711–749)	427 (410–445)	258 (244–273)	157 (146–169)	115 (106–125)	78 (70–86)
2000–2003	958 (931–975)	753 (720–784)	431 (401–462)	250 (226–277)	145 (126–165)	116 (100–133)	85 (72–100)
2004–2007	942 (912–962)	746 (712–777)	458 (429–487)	280 (256–306)	160 (141–181)	120 (104–138)	82 (70–97)
2008–2011	948 (917–968)	691 (654–725)	390 (360–420)	243 (218–269)	168 (148–190)	110 (95–128)	65 (54–79)
Time of death							
No. of infants*	931	1483	1338	887	581	492	361
Birth to 12 hr — no. (%)	834 (89.6)	833 (56.2)	352 (26.3)	158 (17.8)	110 (18.9)	82 (16.7)	84 (23.3)
>12 hr to 28 days — no. (%)	84 (9.0)	539 (36.3)	709 (53.0)	489 (55.1)	310 (53.4)	259 (52.6)	180 (49.9)
>12 hr to 72 hr — no. (%)	36 (3.9)	225 (15.2)	243 (18.2)	149 (16.8)	93 (16.0)	61 (12.4)	47 (13.0)
>72 hr to 7 days — no. (%)	17 (1.8)	83 (5.6)	111 (8.3)	92 (10.4)	49 (8.4)	44 (8.9)	21 (5.8)
8 to 14 days — no. (%)	20 (2.1)	114 (7.7)	163 (12.2)	106 (12.0)	79 (13.6)	80 (16.3)	41 (11.4)
15 to 28 days — no. (%)	11 (1.2)	117 (7.9)	192 (14.3)	142 (16.0)	89 (15.3)	74 (15.0)	71 (19.7)
>28 days — no. (%)	13 (1.4)	111 (7.5)	277 (20.7)	240 (27.1)	161 (27.7)	151 (30.7)	97 (26.9)
29 to 60 days — no. (%)	6 (0.6)	54 (3.6)	138 (10.3)	121 (13.6)	74 (12.7)	73 (14.8)	43 (11.9)
61 to 90 days — no. (%)	4 (0.4)	20 (1.3)	52 (3.9)	40 (4.5)	22 (3.8)	27 (5.5)	19 (5.3)
91 to 120 days — no. (%)	1 (0.1)	8 (0.5)	19 (1.4)	21 (2.4)	21 (3.6)	12 (2.4)	10 (2.8)
>120 days — no. (%)	2 (0.2)	29 (2.0)	68 (5.1)	58 (6.5)	44 (7.6)	39 (7.9)	25 (6.9)

* Information on time of death was missing for two infants.