Original Investigation

# Survival and Morbidity of Preterm Children Born at 22 Through 34 Weeks' Gestation in France in 2011
## Results of the EPIPAGE-2 Cohort Study

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**IMPORTANCE** Up-to-date estimates of the health outcomes of preterm children are needed for assessing perinatal care, informing parents, making decisions about care, and providing evidence for clinical guidelines.

**OBJECTIVES** To determine survival and neonatal morbidity of infants born from 22 through 34 completed weeks' gestation in France in 2011 and compare these outcomes with a comparable cohort in 1997.

**DESIGN, SETTING, AND PARTICIPANTS** The EPIPAGE-2 study is a national, prospective, population-based cohort study conducted in all maternity and neonatal units in France in 2011. A total of 2205 births (stillbirths and live births) and terminations of pregnancy at 22 through 26 weeks' gestation, 3257 at 27 through 31 weeks, and 1234 at 32 through 34 weeks were studied. Cohort data were collected from January 1 through December 31, 1997, and from March 28 through December 31, 2011. Analyses for 1997 were run for the entire year and then separately for April to December; the rates for survival and morbidities did not differ. Data are therefore presented for the whole year in 1997 and the 8-month and 6-month periods in 2011.

**MAIN OUTCOMES AND MEASURES** Survival to discharge and survival without any of the following adverse outcomes: grade III or IV intraventricular hemorrhage, cystic periventricular leukomalacia, severe bronchopulmonary dysplasia, retinopathy of prematurity (stage 3 or higher), or necrotizing enterocolitis (stages 2-3).

**RESULTS** A total of 0.7% of infants born before 24 weeks' gestation survived to discharge: 31.2% of those born at 24 weeks, 59.1% at 25 weeks, and 75.3% at 26 weeks. Survival rates were 93.6% at 27 through 31 weeks and 98.9% at 32 through 34 weeks. Infants discharged home without severe neonatal morbidity represented 0% at 23 weeks, 11.6% at 24 weeks, 30.0% at 25 weeks, 47.5% at 26 weeks, 81.3% at 27 through 31 weeks, and 96.8% at 32 through 34 weeks. Compared with 1997, the proportion of infants surviving without severe morbidity in 2011 increased by 14.4% ($P < .001$) at 25 through 29 weeks and 6% ($P < .001$) at 30 through 31 weeks but did not change appreciably for those born at less than 25 weeks. The rates of antenatal corticosteroid use, induced preterm deliveries, cesarean deliveries, and surfactant use increased significantly in all gestational-age groups, except at 22 through 23 weeks.

**CONCLUSIONS AND RELEVANCE** The substantial improvement in survival in France for newborns born at 25 through 31 weeks' gestation was accompanied by an important reduction in severe morbidity, but survival remained rare before 25 weeks. Although improvement in survival at extremely low gestational age may be possible, its effect on long-term outcomes requires further studies. The long-term results of the EPIPAGE-2 study will be informative in this regard.

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Editorial

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Previous cohort studies[1-7] suggest that survival of infants born before 27 weeks' gestation has improved during the past 2 decades. However, disability rates remain high at these gestational ages.[8-10] Moreover, countries differ substantially in their organization of care, available resources, national laws, and cultural preferences regarding provision of proactive care. Therefore, to provide the best available information for parents and medical staff to use in making treatment decisions, mortality and morbidity must be monitored, and studies should be conducted in countries with different attitudes toward active care at early gestational ages.

By far, most of the important cohort studies[11-13] in the field have focused exclusively on infants born before 27 weeks' gestation. However, even though infants born between 27 and 31 weeks are at lower relative risk of adverse outcomes, they represent a much larger proportion of preterm births. Hence, in absolute numbers, they account for most children with deficits.

We present the results of the EPIPAGE-2 (Etude Epidémiologique sur les Petits Ages Gestationnels 2) study, a national cohort of infants born at a gestational age of 22 through 34 weeks in France in 2011. Our objectives were to study survival and survival without severe neonatal morbidities. We also looked at perinatal interventions and compared the outcomes with those of a similar cohort from 1997, the EPIPAGE-1 study.[13] Our hypothesis was that survival and survival without severe morbidity have improved during the past 15 years in France, except for extremely preterm infants.

## Methods

### Ethics

Recruitment and data collection occurred only after families had received information and agreed to participate in the study. This study was approved by the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés) and by the appropriate ethics committees (Consultative Committee on the Treatment of Information on Personal Health Data for Research Purposes and Committee for the Protection of People Participating in Biomedical Research). Participants provided oral informed consent.

### Study Design and Population Study

EPIPAGE-2 is a national, prospective, population-based study scheduled to follow up preterm children to the age of 12 years. Infants born at 22 through 34 completed weeks' gestation in France were eligible for inclusion. Only one region, which accounts for 2% of all births in France, did not participate. The study began March 28, 2011. Recruitment took place at birth in all maternity units in the participating regions. The number of infants required according to our sample size calculations[14] was provided by an 8-month recruitment period for births at 22 through 26 weeks, a 6-month period for 27 through 31 weeks, and a 5-week period for 32 through 34 weeks. During recruitment, members of the regional coordinating committees visited all maternity units to ensure the identification of all eligible children.

The births in our study population were defined to comprise live births, stillbirths, and terminations of pregnancy for maternal (severe maternal diseases) or fetal (severe growth restriction and oligohydramnios) reasons other than congenital anomalies. In all, 2381 births were eligible at 22 through 26 weeks, 3478 at 27 through 31 weeks, and 1376 at 32 through 34 weeks, with 176, 221, and 142 parental refusals, respectively. The study thus included 2205 births at 22 through 26 weeks, 3257 at 37 through 31 weeks, and 1234 at 32 through 34 weeks. Total births in the 25 French regions in 2011 (National Institute of Statistics and Economic Studies; http://www.insee.fr/fr/) were used to estimate preterm birth rates, taking into account months of inclusion and differences in recruitment periods according to gestational age at birth.

### Data Collection

In each center, one obstetric and one pediatric study coordinator were responsible for data acquisition, validation, and quality control. Data were collected from medical records and obstetric and neonatal staff. Data on stillbirths and terminations of pregnancy were collected at the time of delivery. Data on live-born infants were collected prospectively during hospitalization until discharge or death. Gestational age was defined as the best obstetric estimate combining last menstrual period and ultrasonogram assessment. Extensive data were collected about pregnancy, delivery, and the neonatal period to investigate pregnancy complications, decisions about terminations of pregnancy, the child's condition at birth, neonatal diseases, organization of care, treatment, and attitudes toward care. Only selected perinatal data were considered for this study: level of care of the institution, antenatal corticosteroid use, vaginal or cesarean delivery, indicated preterm delivery (defined as a birth after induction of labor or cesarean delivery before the onset of labor), and use of surfactants and postnatal corticosteroids. Questionnaires were completed online, with a secure interface that protected the confidentiality and privacy of data and personal information. The EPIPAGE coordination team used a centralized system to monitor and validate inclusion and data collection at the national level.

### Outcome Measures

The primary outcome was infant survival, defined as the number of children discharged home alive. The secondary outcome was survival to discharge without severe neonatal morbidity. Severe neonatal morbidity was defined as any of the following outcomes: severe intraventricular hemorrhage (IVH), defined as IVH associated with ventricular dilatation (grade III IVH) and intraparenchymal hemorrhage (ie, large unilateral parenchymal hyperdensity or a large unilateral porencephalic cyst)[15]; cystic periventricular leukomalacia (cPVL) (ie, periventricular white matter echolucencies at ultrasonography); stages II and III necrotizing enterocolitis, according to the staging of Bell et al[16]; stage 3 or higher retinopathy of prematurity, according to the international classification[17] and/or laser treatment; and/or severe bronchopulmonary dysplasia (BPD), defined as administration of oxygen for at least 28 days plus need for 30% or more oxygen and/or mechanical ventilatory support or continuous positive airway pressure at 36

weeks' postmenstrual age.[18] Among infants admitted to the neonatal intensive care unit (NICU), 98.0% of survivors born before 33 weeks, 88.0% of those born at 33 weeks, and 66.0% of those born at 34 weeks had at least one cranial ultrasonogram assessment. Survivors at 33 and 34 weeks without cranial ultrasonogram assessment were considered not to have severe cerebral lesions, and those with no funduscopic examination were considered not to have severe retinopathy of prematurity.

### Comparison of French Birth Cohorts Between 1997 and 2011

In 1997, the EPIPAGE-1 study, a comparable prospective, population-based cohort study, took place in 9 regions of France.[13,19] Eligible infants for this comparison are those born alive between 22 and 34 weeks' gestation from the 1997 and 2011 cohorts in the same 9 regions. Outcome measures are survival to discharge and survival without neonatal morbidity. The latter was defined as above, except for BPD (oxygen supplementation at 36 weeks' postmenstrual age) because information on its severity was not available in 1997. Cohort data were collected from January 1 through December 31, 1997, and from March 28 through December 31, 2011.[14] Analyses for 1997 were run for the entire year and then separately for April to December; the rates for survival and morbidities did not differ. Data are therefore presented for the whole year in 1997 and the 8-month and 6-month periods in 2011.

### Statistical Analysis

Data reported on the birth certificate (ie, gestational age at birth, vital status at birth, and neonatal death) were available and usable without parental consent for children not included in the study. We compared the survival of the participating and nonparticipating (because of parent refusal) newborns. Then, for the infants whose parents agreed to participate, we analyzed survival to discharge, severe neonatal morbidity, survival without severe morbidity, and some obstetric and neonatal interventions, according to gestational age. To examine trends over time, we compared survival and neonatal morbidity in the EPIPAGE-1 study[19] with those in the EPIPAGE-2 study according to gestational age. For each week of gestation, we report exact 95% binomial CIs of survival rates and their differences. All tests were 2-sided; $P < .05$ was considered statistically significant. All statistical analyses were performed with SAS statistical software, version 9.3 (SAS Institute Inc).

## Results

### Preterm Birth Rates

In 2011, preterm birth rates were 4.4 per 1000 total stillbirths and live births and 2.1 per 1000 live births before 27 weeks' gestation, 8.4 and 7.5 at 27 through 31 weeks, and 17.8 and 17.3 at 32 through 34 weeks, respectively.

### Comparison of Study Participants and Nonparticipants

Participation rates were 92.6% among infants born at 22 through 26 weeks, 93.6% among those at 27 through 31 weeks, and 89.7% among those at 32 through 34 weeks. In each gestational age group, the proportion of live births was slightly higher among participants than nonparticipants. Survival among live births did not differ significantly between the 2 groups (eTable 1 in the Supplement).

### Status at Birth and Perinatal Deaths

The proportion of live-born infants increased with gestational age from 13.5% at 22 weeks to 98.5% at 34 weeks (**Table 1**). Only one infant born at 22 through 23 weeks (ie, 0.1% of all births and 0.7% of live births) survived to discharge (Table 1). Survival rates were 14.4% of all births and 31.2% of live births at 24 weeks, 41.8% and 59.1% at 25 weeks, 59.6% and 75.3% at 26 weeks, 73.7% and 86.3% at 27 through 28 weeks, 88.0% and 96.6% at 29 through 31 weeks, and 96.7% and 98.9% at 32 through 34 weeks, respectively (Table 1). Among infants who died, the proportion whose deaths followed a decision to limit intensive care varied from 80.9% at 22 through 24 weeks and 70.3% at 25 through 26 weeks to 57.0% at 27 through 31 weeks. The median age at death was the day of birth for infants born at 22 through 24 weeks, 5 days (interquartile range, 1-16 days) for those born at 25 through 26 weeks, and 7 days (interquartile range, 1-22 days) for those born at 27 through 31 weeks.

### Perinatal Interventions

Among the live-born infants at 22 weeks, 36.2% were born in level III hospitals compared with 61.8% at 23 weeks, 77.4% at 24 weeks, 85.0% at 25 through 26 weeks, 84.8% at 27 through 31 weeks, and 50.1% at 32 through 34 weeks (**Table 2**). Among extremely preterm infants not born in a level III hospital, 54.3% were postnatally transferred to a NICU; this proportion varied from 4.3% at 22 through 23 weeks to 45.3% at 24 weeks and 90.7% at 25 through 26 weeks. Postnatal transfers to a NICU reached 91.8% at 27 through 29 weeks but decreased to 56.3% at 30 through 31 weeks and 17.0% at 32 through 34 weeks. The percentage of infants exposed to antenatal corticosteroids was very low at 22 (1.8%) and 23 (12.3%) weeks but increased to 56.7% at 24 weeks and 78.4% at 25 through 26 weeks (Table 2). Cesarean rates were 6.3% at 22 through 23 weeks and 13.5% at 24 weeks compared with 34.0% at 25 weeks and 59.9% at 26 weeks; this rate reached 69.8% at 27 through 31 weeks. Few of the infants born at 22 through 23 weeks were admitted to NICUs (6.1%); this percentage increased to 60.8% at 24 weeks, 91.9% at 25 weeks, 95.6% at 26 weeks, and 98.9% at 27 through 31 weeks. Among infants admitted to the NICU, 96.7% of those born at 24 through 26 weeks received surfactant and 24.0% received postnatal corticosteroids.

### Neonatal Morbidity

Of survivors at 24 through 26 weeks, 12.9% had severe IVH, 2.4% had cPVL, 25.6% had severe BPD, 6.0% had retinopathy of prematurity stage 3 or higher, and 5.1% had stage 2 or 3 necrotizing enterocolitis (**Table 3**). In this group, 299 infants (59.2% of survivors and 34.1% of live births) were discharged home without severe neonatal morbidity. The percentage of such survivors ranged from 0% at 23 weeks to 65.3% (47.5% of live births) at 26 weeks (**Figure 1**). Of the 206 infants who survived with severe neonatal conditions, 23.8% had 2 or more conditions. Of survivors at 27 through 31 weeks, 2254 (87.6%; 81.3%

Table 1. Vital Status at Birth, Deaths, and Survival by Gestational Age in 2011

| Gestational Age, wk | No. (%) of Events | | | | | | |
|---|---|---|---|---|---|---|---|
| | All Infants (N = 6696) | TOP[a] (n = 214) | Stillbirths[a] (n = 1313) | Live Births[a] (n = 5169) | Deaths in Maternity Ward[b] (n = 289) | Deaths in NICU[b] (n = 413) | Survival to Discharge[b,c] (n = 4467) |
| 22 | 430 | 53 (12.3) | 319 (74.2) | 58 (13.5) | 56 (96.6) | 2 (3.4) | 0 |
| 23 | 414 | 43 (10.4) | 282 (68.1) | 89 (21.5) | 82 (92.1) | 6 (6.7) | 1 (1.1) [0-3.3] |
| 24 | 404 | 40 (9.9) | 178 (44.1) | 186 (46.0) | 73 (39.2) | 55 (29.6) | 58 (31.2) [24.5-37.8] |
| 25 | 435 | 28 (6.4) | 99 (22.8) | 308 (70.8) | 25 (8.1) | 101 (32.8) | 182 (59.1) [53.6-64.6] |
| 26 | 522 | 24 (4.6) | 85 (16.3) | 413 (79.1) | 18 (4.4) | 84 (20.3) | 311 (75.3) [71.1-79.5] |
| 22-26 | 2205 | 188 (8.5) | 963 (43.7) | 1054 (47.8) | 254 (24.1) | 248 (23.5) | 552 (52.4) [49.4-55.4] |
| 27 | 478 | 11 (2.3) | 67 (14.0) | 400 (83.7) | 9 (2.3) | 62 (15.5) | 329 (82.3) [78.5-86.0] |
| 28 | 526 | 6 (1.1) | 63 (12.0) | 457 (86.9) | 6 (1.3) | 40 (8.8) | 411 (89.9) [87.2-92.7] |
| 29 | 561 | 4 (0.7) | 48 (8.6) | 509 (90.7) | 6 (1.2) | 17 (3.3) | 486 (95.5) [93.7-97.3] |
| 30 | 761 | 5 (0.7) | 75 (9.9) | 681 (89.5) | 2 (0.3) | 19 (2.8) | 660 (96.9) [95.6-98.2] |
| 31 | 931 | 0 | 69 (7.4) | 862 (92.6) | 8 (0.9) | 18 (2.1) | 836 (97.0) [95.8-98.1] |
| 27-31 | 3257 | 26 (0.8) | 322 (9.9) | 2909 (89.3) | 31 (1.1) | 156 (5.4) | 2722 (93.6) [92.7-94.5] |
| 32 | 281 | 0 | 10 (3.6) | 271 (96.4) | 1 (0.4) | 4 (1.5) | 266 (98.2) [96.6-99.8] |
| 33 | 363 | 0 | 9 (2.5) | 354 (97.5) | 1 (0.3) | 2 (0.6) | 351 (99.2) [98.2-100] |
| 34 | 590 | 0 | 9 (1.5) | 581 (98.5) | 2 (0.3) | 3 (0.5) | 576 (99.1) [98.4-99.9] |
| 32-34 | 1234 | 0 | 28 (2.3) | 1206 (97.7) | 4 (0.3) | 9 (0.7) | 1193 (98.9) [98.3-99.5] |

Abbreviations: NICU, neonatal intensive care unit; TOP, termination of pregnancy for maternal and fetal reasons (other than congenital anomalies).

[a] Related to all births.

[b] Related to live births.

[c] Numbers in brackets are 95% binomial CIs for the percentage of patients.

of live births) were discharged home without severe neonatal morbidity; the percentage of survivors ranged from 71.9% (57.6% of live births) at 27 weeks to 93.5% (90.6% of live births) at 31 weeks (Figure 1). Among the 320 infants with severe neonatal morbidities, 8.4% had 2 or more morbidities. At 32 through 34 weeks, 1080 infants (97.9% of survivors and 96.8% of live births) were discharged home without severe neonatal morbidity. One infant had 2 severe conditions.

### Trends Between 1997 and 2011

Among infants born alive at 22 through 23 weeks in the 9 regions studied in 1997, none survived in 1997 or 2011, and the chance of survival at 24 weeks did not change between the studies (**Figure 2**A and eTable 2 in the Supplement). Survival increased in these regions by 11.2% (95% CI, −0.5% to 22.9%) at 25 weeks, 18.1% (95% CI, 8.2% to 28.1%) at 26 weeks, 12.8% (95% CI, 4.8% to 20.8%) at 27 weeks, 12.3% (95% CI, 6.1% to 18.6%) at 28 weeks, 7.1% (95% CI, 2.7% to 11.5%) at 29 weeks, 4.7% (95% CI, 1.4% to 8.0%) at 30 weeks, and 2.1% (95% CI, −0.2% to 4.4%) at 31 weeks. Although median age at death did not change at 22 through 24 weeks, it increased significantly at 25 through 26 weeks. Between 1997 through 2011, the rates of antenatal corticosteroid use, indicated preterm deliveries, and surfactant use increased significantly in all gestational-age groups, except at 22 through 23 weeks (Figure 2C-E and eTable 3 in the Supplement).

Survival without neonatal morbidity did not change significantly at 24 weeks between 1997 (2.4%) and 2011 (7.4%) (Figure 2B). It increased by 16.2% (95% CI, 6.7% to 25.8%) at 25 weeks, 19.0% (95% CI, 9.1% to 28.8%) at 26 weeks, 16.3% (95% CI, 6.4% to 26.2%) at 27 weeks, 17.8% (95% CI, 9.2% to 26.5%) at 28 weeks, 16.6% (95% CI, 8.7% to 24.5%) at 29 weeks, 6.3% (95% CI, 0.7% to 11.8%) at 30 weeks, and 5.9% (95% CI, 1.8% to 10.1%) at 31 weeks. Among survivors at 24 through 26 weeks, the rates of necrotizing enterocolitis ($P$ = .005), BPD ($P$ = .004), cPVL, and severe retinopathy of prematurity decreased between 1997 and 2011, although not significantly for the cPVL ($P$ = .07) and severe retinopathy of prematurity ($P$ = .11) (eTable 4 in the Supplement). At 27 through 31 weeks, the prevalence of cPVL decreased by 3% ($P$ < .001) and BPD by 4% ($P$ < .001). Only cPVL decreased among infants born at 32 through 34 weeks ($P$ = .03) (eTable 4 in the Supplement).

## Discussion

The results of the EPIPAGE-2 study, a national, prospective, population-based cohort study of births at 22 through 34 weeks' gestation, indicate that survival and survival without severe neonatal morbidity improved significantly between 1997 and 2011 for infants born at 25 through 31 weeks. By contrast, neither survival nor survival without morbidity improved for infants born before 25 weeks.

The strengths of the EPIPAGE-2 study include the population-based cohort design and prospective enrollment of infants born prematurely in France in 2011. Standardized definitions of outcomes and systematic and prospective collection of all information available (eg, all cranial ultrasonograms) from a national sample of more than 8000 preterm births (22-34 weeks' gestation) allowed us to look at the effects associated with a wide range of gestational ages on survival and on major neonatal morbidities in our population. The accuracy of the gestational age estimates was improved by the very high rate (>98%) of women with early ultrasonogram assessments.

Table 2. Perinatal Characteristics and Obstetric and Neonatal Interventions by Gestational Age in 2011[a]

| Gestational Age, wk | Multiple Birth[b] | Birth Weight, Median (IQR), g[c] | Birth in Level III Maternity[b] | Antenatal Corticosteroid Use[b] | Indicated Preterm Delivery[b,d] | Cesarean Delivery[b] | Surfactant Use[e] | Postnatal Corticosteroid Use[f] | Length of Hospital Stay, Median (IQR), wk[e] |
|---|---|---|---|---|---|---|---|---|---|
| 22 | 20/58 (34.5) | 490 (438-523) | 21/58 (36.2) | 1/57 (1.8) | 8/57 (14.0) | 5/57 (8.8) | 1/2 (50.0) | 0/2 (0) | 0 |
| 23 | 31/89 (34.8) | 570 (510-620) | 55/89 (61.8) | 10/81 (12.3) | 8/88 (9.1) | 4/87 (4.6) | 5/7 (71.4) | 0/7 (0) | 147 |
| 24 | 52/186 (28.0) | 680 (618-730) | 144/186 (77.4) | 101/178 (56.7) | 20/182 (11.0) | 24/178 (13.5) | 108/112 (96.4) | 30/109 (27.5) | 119 (109-141) |
| 25 | 121/308 (39.3) | 760 (700-830) | 258/308 (83.8) | 225/298 (75.5) | 71/303 (23.4) | 103/303 (34.0) | 270/278 (97.1) | 75/273 (27.5) | 104 (90-123) |
| 26 | 114/413 (27.6) | 860 (750-940) | 355/413 (86.0) | 328/407 (80.6) | 153/400 (38.3) | 246/411 (59.9) | 375/389 (96.4) | 78/379 (20.6) | 92 (82-105) |
| 22-26 | 338/1054 (32.1) | 750 (633-860) | 833/1054 (79.0) | 665/1021 (65.1) | 260/1030 (25.2) | 382/1036 (36.9) | 759/788 (96.3) | 183/770 (23.8) | 98 (87-119) |
| 27 | 135/400 (33.8) | 970 (806-1070) | 347/400 (86.8) | 315/389 (81.0) | 183/382 (47.9) | 277/396 (69.9) | 347/388 (89.4) | 53/373 (14.2) | 81 (70-98) |
| 28 | 142/457 (31.1) | 1090 (950-1220) | 400/457 (87.5) | 386/452 (85.4) | 224/446 (50.2) | 320/456 (70.2) | 364/448 (81.3) | 32/432 (7.4) | 70 (62-84) |
| 29 | 149/509 (29.3) | 1240 (1050-1370) | 449/509 (88.2) | 424/503 (84.3) | 274/492 (55.7) | 356/508 (70.1) | 327/501 (65.3) | 23/487 (4.7) | 59 (51-70) |
| 30 | 208/681 (30.5) | 1370 (1160-1530) | 593/681 (87.1) | 561/668 (84.0) | 376/655 (57.4) | 488/678 (72.0) | 312/673 (46.4) | 12/658 (1.8) | 50 (43-60) |
| 31 | 294/862 (34.1) | 1540 (1310-1710) | 678/862 (78.7) | 713/841 (84.8) | 465/827 (56.2) | 578/854 (67.7) | 324/841 (38.5) | 8/830 (1.0) | 41 (36-50) |
| 27-31 | 928/2909 (31.9) | 1260 (1040-1500) | 2467/2909 (84.8) | 2399/2853 (84.1) | 1522/2802 (54.3) | 2019/2892 (69.8) | 1674/2851 (58.7) | 128/2780 (4.6) | 55 (44-70) |
| 32 | 125/271 (46.1) | 1710 (1520-1939) | 162/271 (59.8) | 220/264 (83.3) | 130/257 (50.6) | 177/269 (65.8) | 54/264 (20.5) | 2/261 (0.8) | 34 (28-40) |
| 33 | 124/354 (35.0) | 1920 (1710-2120) | 175/354 (49.4) | 271/345 (78.6) | 163/336 (48.5) | 202/354 (57.1) | 57/346 (16.5) | 0/341 (0) | 26 (21-32) |
| 34 | 197/581 (33.9) | 2150 (1920-2370) | 267/581 (46.0) | 376/569 (66.1) | 265/564 (47.0) | 280/578 (48.4) | 38/561 (6.8) | 0/563 (0) | 16 (12-22) |
| 32-34 | 446/1206 (37.0) | 1985 (1720-2230) | 604/1206 (50.1) | 867/1178 (73.6) | 558/1157 (48.2) | 659/1201 (54.9) | 149/1171 (12.7) | 2/1165 (0.2) | 23 (16-32) |

Abbreviation: IQR, interquartile range.

[a] Data are presented as number of events/number in group (percentage) unless otherwise indicated. Denominators vary according to the number of missing data for each variable.

[b] Related to live births.

[c] Birth weight is missing for 6 infants born at 23 through 26 weeks' gestation and 2 infants born at 27 through 31 weeks' gestation.

[d] Indicated preterm delivery: birth after induction of labor or cesarean delivery before the onset of labor.

[e] Estimated in days among survivors: only for length of hospital stay.

[f] Related to infants admitted to neonatal intensive care units: only for surfactant use and postnatal corticosteroid use.

One limitation is that 7% of eligible infants were not included because of parental refusal. However, the survival status of all patients, including those who refused to participate, was available. Furthermore, the percentage of survival in these 2 groups did not differ significantly. Therefore, the effect of this selection was very slight.

These 2 EPIPAGE studies[13,19] made it possible to determine the changes in mortality and morbidity between 1997 through 2011. We studied neonatal conditions known to be prognostic for long-term outcomes. Although the studies had a common design, more extensive data were collected in 2011 than in 1997. Hence, we may have underestimated changes between the 2 periods for survival without morbidity and morbidity rates in general. However, because we restricted our comparisons to severe neonatal conditions, defined similarly in each study, we assume that the influence of this difference was slight.

One important result of our study is that less than 1% of infants born at 22 through 23 weeks survived. In this population, 80.9% of deaths occurred after a decision to limit intensive care, mostly within the first day of life. The general policy in France is not to intervene before 24 weeks' gestation; infants born earlier receive palliative but not intensive care.[20] We compared French results with those of large contemporary international studies[1,2,4,6,7,21] conducted in the middle to late 2000s (eTable 5 in the Supplement). The more active perinatal management at the limit of viability in other countries has resulted in higher survival rates than those in our population at extremely preterm gestational ages.[1,2,4,6,7] At 24 weeks, survival remained low in France, reflecting the lack of consensus and heterogeneity of perinatal management for these infants. In this group, as among those born at 22 through 23 weeks, deaths occurred within a day of birth after a decision to limit intensive care. This timing contrasts with the timing of death in those countries that report high rates of perinatal interventions and survival.[1,2,6,7] Active perinatal interventions and survival became more frequent in France at 25 weeks, but survival rates remained higher in the United States, Japan, and Sweden up to a gestational age of 27 weeks.[5,6]

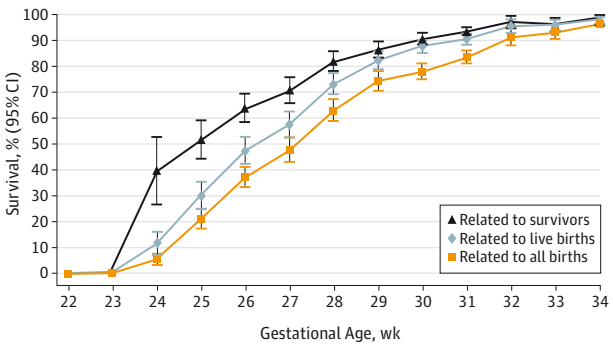
Table 3. Severe Neonatal Morbidity According to Gestational Age Among Survivors to Discharge in 2011[a]

| Gestational Age, wk | No. of Events/No. in Group (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade III IVH or IPH | Cystic PVL | Severe BPD | Severe ROP | Severe NEC | No. of Severe Neonatal Morbidities | | |
| | | | | | | 0 | 1 | ≥2 |
| 23 | 0/1 (0) | 0/1 (0) | 1/1 (100.0) | 0/1 (0) | 1/1 (100.0) | 0/1 (0) | 0/1 (0) | 1/1 (100.0) |
| 24 | 13/58 (22.4) | 1/58 (1.7) | 19/51 (37.3) | 10/58 (17.2) | 3/57 (5.3) | 21/51 (41.2) | 17/51 (33.3) | 13/51 (25.5) |
| 25 | 26/180 (14.4) | 4/182 (2.2) | 47/168 (28.0) | 17/180 (9.4) | 10/181 (5.5) | 90/165 (54.5) | 57/165 (34.5) | 18/165 (10.9) |
| 26 | 32/310 (10.3) | 8/311 (2.6) | 64/292 (21.9) | 6/308 (1.9) | 14/310 (4.5) | 188/288 (65.3) | 83/288 (28.8) | 17/288 (5.9) |
| 23-26 | 71/549 (12.9) | 13/552 (2.4) | 131/512 (25.6) | 33/547 (6.0) | 28/549 (5.1) | 299/505 (59.2) | 157/505 (31.1) | 49/505 (9.7) |
| 27 | 26/326 (8.0) | 9/327 (2.8) | 49/311 (15.8) | 4/325 (1.2) | 17/323 (5.3) | 220/306 (71.9) | 74/306 (24.2) | 12/306 (3.9) |
| 28 | 16/404 (4.0) | 10/406 (2.5) | 30/391 (7.7) | 1/408 (0.2) | 19/402 (4.7) | 315/380 (82.9) | 58/380 (15.3) | 7/380 (1.8) |
| 29 | 24/477 (5.0) | 10/482 (2.1) | 16/466 (3.4) | 1/482 (0.2) | 17/483 (3.5) | 399/459 (86.9) | 57/459 (12.4) | 3/459 (0.7) |
| 30 | 17/651 (2.6) | 10/654 (1.5) | 13/644 (2.0) | 0/655 (0) | 21/651 (3.2) | 572/629 (90.9) | 56/629 (8.9) | 1/629 (0.2) |
| 31 | 16/819 (2.0) | 9/823 (1.1) | 12/821 (1.5) | 1/830 (0.1) | 19/831 (2.3) | 748/800 (93.5) | 48/800 (6.0) | 4/800 (0.5) |
| 27-31 | 99/2677 (3.7) | 48/2692 (1.8) | 120/2633 (4.6) | 7/2700 (0.3) | 93/2690 (3.5) | 2254/2574 (87.6) | 293/2574 (11.4) | 27/2574 (1.0) |
| 32 | 2/251 (0.8) | 3/253 (1.2) | 0/261 (0) | 0/261 (0) | 2/260 (0.8) | 236/242 (97.5) | 6/242 (2.5) | 0/242 (0) |
| 33 | 1/350 (0.3) | 4/350 (1.1) | 0/342 (0) | 0/345 (0) | 6/339 (1.8) | 317/328 (96.6) | 11/328 (3.4) | 0/328 (0) |
| 34 | 4/574 (0.7) | 2/574 (0.3) | 0/560 (0) | 0/564 (0) | 2/544 (0.4) | 527/533 (98.9) | 5/533 (0.9) | 1/533 (0.2) |
| 32-34 | 7/1175 (0.6) | 9/1177 (0.8) | 0/1163 (0) | 0/1170 (0) | 10/1143 (0.9) | 1080/1103 (97.9) | 22/1103 (2.0) | 1/1103 (0.1) |

Abbreviations: BPD, bronchopulmonary dysplasia; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

[a] Denominators vary according to the number of missing data for each variable.

Figure 1. Survival Without Severe Neonatal Morbidity in 2011

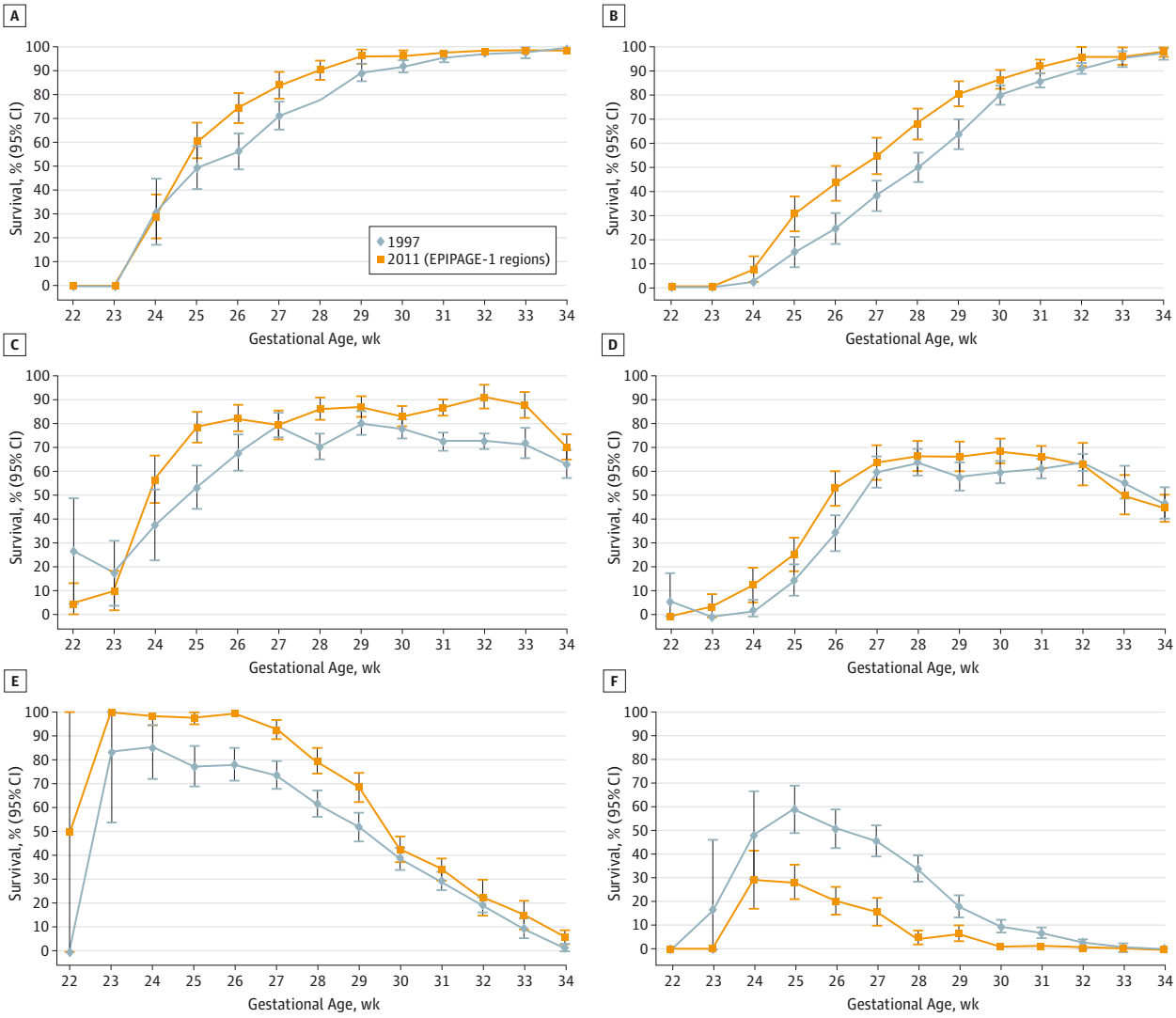



For each week of gestation, percentages and exact 95% binomial CIs (error bars) are presented.

International comparisons emphasize that the potential for survival among extremely preterm infants is 10% to 50% higher than our results. They also suggest that active management of extremely preterm infants can improve survival for those born at higher gestational ages. In France, the extension of withholding care to less premature infants, because of fears about immediate and long-term adverse outcomes, might also explain our results at 25 through 27 weeks. However, results of comparisons such as those noted above should be interpreted with caution because differences in gestational age measurement and in the distinction between stillbirths and live births cannot be excluded.[22] One way to clarify the role of these issues would be to design multinational cohort studies with standardized methods. In addition, meta-analysis of outcomes using patient-level data might allow better assessment of country-level differences in outcomes.

There is a widespread consensus that the aim of neonatal care should be to resuscitate infants with a reasonable likelihood of an acceptable quality of life, but identification of strategies for better outcomes remains difficult. Uncertainty about long-term outcomes at the limit of viability influences treatment decisions at extremely low gestational ages in France. The results of previous studies[6,23-25] of trends in short-term morbidity and longer-term outcomes of infants born at gestational ages close to this limit make it difficult to predict the effect of a more proactive management of these infants on their survival without morbidity. Hence, consideration of this potential effect must examine the possible and problematic nature of the trade-off between improved survival and increased risk of severe long-term adverse health outcomes for infants born before 25 weeks.

Figure 2. Comparison of Survival Rates and Obstetric and Neonatal Interventions in 1997 and 2011




For each week of gestation, percentages and exact 95% binomial CIs (error bars) are presented. A, Survival to discharge; B, survival to discharge without morbidity; C, antenatal corticosteroid use; D, cesarean deliveries; E, surfactant use; and F, postnatal corticosteroid use.

Results of our trend study during a 15-year period (1997-2011) reveal that survival without morbidity increased by 14.1% for infants born at 25 through 29 weeks. This finding indicates that 1 of every 7 infants had a more favorable outcome in 2011 compared with 1997. Hence, the total number of children surviving without short-term and perhaps also long-term severe adverse outcomes has increased over time.

## Conclusions

Few other population-based studies from around the world provide up-to-date estimates of short-term prognosis of extremely, very, and moderately preterm infants and of changes during the past decade. International comparisons help to estimate the potential for survival and to identify appropriate interventions; they thus reveal areas for improvement in each country. In particular, they reveal that improvement in survival at extremely low gestational age is possible in France and in countries with similar practices. This finding should encourage health care professionals to reassess their attitudes toward care at extremely low gestational ages. This reassessment should include a complete analysis of neonatal morbidity and long-term sequelae, which have not yet been sufficiently evaluated, although they remain important factors in decision making. EPIPAGE-2 should provide further information on them as the children it studies age. Finally, specificities in the organization of care, health policies, laws, and available resources of each country must also be part of this discussion.

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