Volume of Neonatal Care and Survival without Disability at 2 Years in Very Preterm Infants: Results of a French National Cohort Study

Thomas Desplanches, RM, MSc[1,2], Béatrice Blondel, PhD[1], Andrei Scott Morgan, MD, PhD[1], Antoine Burguet, MD, PhD[1,3], Monique Kaminski, MSc[1], Bénédicte Lecomte, MD[4], Laetitia Marchand-Martin, MSc[1], Jean-Christophe Rozé, MD, PhD[5], Paul Sagot, MD, PhD[2], Patrick Truffert, MD, PhD[6], Jennifer Zeitlin, PhD[1], Pierre-Yves Ancel, MD, PhD[1,7], and Jeanne Fresson, MD, PhD[1,8]

Objectives To investigate the relation between neonatal intensive care unit (NICU) volume and survival, and neuromotor and sensory disabilities at 2 years in very preterm infants.

Study design The EPIPAGE-2 (Etude Epidémiologique sur les Petits Âges Gestationnels-2) national prospective population-based cohort study was used to include 2447 babies born alive in 66 level III hospitals between 24 and 30 completed weeks of gestation in 2011. The outcome was survival without disabilities (levels 2-5 of the Gross Motor Function Classification System for cerebral palsy with or without unilateral or bilateral blindness or deafness). Units were grouped in quartiles according to volume, defined as the annual admissions of very preterm babies. Multivariate logistic regression analyses with population average models were used.

Results Survival at discharge was lower in hospitals with lower volumes of neonatal activity (aOR 0.55, 95% CI 0.33-0.91). Survival without neuromotor and sensory disabilities at 2 years increased with hospital volume, from 75% to 80.7% in the highest volume units. After adjustment for gestational age, small for gestational age, sex, maternal age, infertility treatment, multiple pregnancy, principal cause of prematurity, parental socioeconomic status, and mother's country of birth, survival without neuromotor or sensory disabilities was significantly lower in hospitals with a lower volume of neonatal activity (aOR 0.60, 95% CI 0.38-0.95) than in the highest quartile hospitals.

Conclusions These results suggest that lower neonatal intensive care unit volume is associated with lower survival without an increase in disabilities at 2 years. These results could be useful to generate improvements of perinatal regionalization. *(J Pediatr 2019;213:22-9)*.

Studies on regionalization of care have shown that mortality and severe neonatal morbidity of very low birth weight (VLBW) or very preterm (VPT) infants is lower when birth occurs at highly specialized hospitals.[1,2] In most developed countries, it is recommended that VLBW and VPT infants be born in specialized hospitals, generally designated as level III neonatal intensive care unit (NICU) hospitals.[3-6]

Several studies have used hospital volume as an indicator of quality of care, and found that neonatal care at high-volume centers was associated with lower in-hospital mortality of VLBW and VPT infants.[7-12] However, some of these studies[11,12] also found a higher rate of severe neonatal morbidity in high volume hospitals, suggesting that their survivors may be at increased risk of disability in survivors. Studying longer term outcomes at 2 years is needed to determine whether the improvement in survival is followed by an increase in disabilities, providing valuable data for policy makers. In addition, it is worth testing whether these associations, seen primarily in the US and in VLBW babies, exist in other countries and in VPT babies.

Perinatal regionalization has been in place in France since 1998.[13] Level III hospitals are defined as the highest level of care for preterm birth and must have a neonatal intensive care unit (NICU), with the permanent presence of a qualified pediatrician trained in neonatology.[14] In 2011, more than 80% of preterm births at 24^{+0} to 30^{+6} completed weeks of gestation were managed in

ASQ	Ages and Stages Questionnaire
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
EPIPAGE-2	Etude EPIdémiologique sur les Petits Âges GEstationnels
NICU	Neonatal intensive care unit
Q	Quartile
SGA	Small for gestational age
VLBW	Very low birth weight
VPT	Very preterm

From the [1]Obstetrical, Perinatal, and Pediatric Epidemiology Team, Epidemiology and Biostatistics Sorbonne Paris Cité Research Center (U1153), INSERM, Paris Descartes University, Paris, France; [2]CHRU Dijon, Department of Gynecology, Obstetrics, Fetal Medicine, and Infertility, University of Burgundy and Franche-Comté, Dijon, France; [3]Department of Neonatal Pediatrics, Dijon University Hospital, Dijon, France; [4]Estaing University Hospital, Clermont-Ferrand, France; [5]Pediatric Intensive Care Unit, Mothers' and Children's Hospital, Nantes Teaching Hospital, Nantes, France; [6]Neonatal Intensive Care Unit, Jeanne de Flandre Hospital, CHRU Lille, Lille, France; [7]Clinical Research Unit, Center for Clinical Investigation P1419, CHU Cochin Broca Hôtel-Dieu, Paris, France; and [8]CHRU Nancy, Department of Medical Information, Nancy, France

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a level III hospital.[15] Previous French studies on regionalization are relatively outdated,[16,17] and none has investigated the effect of hospital volume.

Our objectives were to investigate the association of hospital volume with survival at discharge without severe neonatal morbidity, and survival at 2 years of corrected age without neuromotor or sensory disabilities, among infants born at 24^{+0} to 30^{+6} weeks of gestation in tertiary hospitals. We hypothesized that there would be higher survival without disability in VPT children born in hospitals that managed a high volume of premature newborns. We also investigated to what extent the implementation of evidence-based practices varied by NICU volumes, potentially contributing to the health outcomes of VPT children.

Methods

The prospective population-based EPIPAGE-2 cohort (Etude Epidémiologique sur les Petits Âges Gestationnels) included all births occurring between 22 and 34 completed weeks of gestation in the 546 maternity units of 25 French regions from March to December in 2011. Recruitment lasted 8 months for infants born at 22-26 weeks and 6 months for those born at 27-31 weeks of gestation. At 2 years of corrected age, clinical data were collected through 2 standardized questionnaires: one completed by the referring pediatrician and the other by the parents. Details about ethical approval, the design, and methods have been described previously.[18,19]

We restricted our analyses to babies who were born alive in tertiary centers between 24 and 30 weeks of gestation. We excluded neonates born after 30 weeks because the French recommendations allow for the management of these births in lower level hospitals. Newborns with lethal malformations (eg, anencephaly and bilateral renal agenesis) or antenatal decision not to resuscitate were also excluded. All survivors were enrolled in follow-up if parents consented at 2 years of corrected age.

Volume was defined as the total number of babies below 31 weeks of gestation admitted to each hospital NICU during 2011. This number was obtained from the national hospital discharge database ("Programme de médicalisation du système d'information" used to determine the activity-based funding of French hospitals). We created 4 groups of hospitals using the 25th, 50th, and 75th percentiles of volume. Hospitals in the highest quartile (Q4) were defined as high-volume units. Infants were allocated to the first level 3 unit in which they were hospitalized for 48 consecutive hours, or, when infants died in the delivery room, the NICU in connection with the obstetric unit.

Studied outcomes were survival at discharge, survival at discharge without severe neonatal morbidity, survival without sensorimotor disabilities at 2 years of age, and psychomotor development outcome at 2 years. Severe neonatal morbidity was defined by 1 or more of the following complications: severe bronchopulmonary dysplasia, defined as administration of oxygen for at least 28 days plus need for 30% or more oxygen and/or mechanical ventilation or continuous positive airway pressure at 36 weeks of postmenstrual age, severe intraventricular hemorrhage, defined as intraventricular hemorrhage associated with ventricular dilation (grade III, IV) and/or intraparenchymal hemorrhage, cystic periventricular leukomalacia, Bell stage II or III necrotizing enterocolitis, and stage 3 or higher retinopathy of prematurity.[18]

Neuromotor and sensory disabilities included 2 outcomes: cerebral palsy and sensory disability. We used the diagnostic criteria previously established by the Surveillance of Cerebral Palsy in Europe network to define cerebral palsy,[20] and the 5 level Gross Motor Function Classification System to classify motor ability.[21] A child had a disability if he/she had cerebral palsy, Gross Motor Function Classification System level 2-5, or unilateral or bilateral deafness or blindness. Psychomotor development outcome at 2 years of age was assessed using the second version of the Ages and Stages Questionnaire (ASQ),[22] and we analyzed the data if parents filled out this document when their child was between 22 and 26 months of corrected age and if the child did not have cerebral palsy or sensory impairments. ASQ evaluates 5 domains of child development: communication, gross motor, fine motor, problem-solving, and personal-social. We considered a child as below threshold if he/she scored lower than 2 SDs from the mean in at least 1 domain.[22]

We considered the following maternal characteristics: maternal age, maternal country of birth, and parents' socioeconomic status (the highest occupational status of the mother and the father, or mother only if a single parent). Pregnancy characteristics were parity, infertility treatment, multiple pregnancy, antenatal steroids, antenatal transfer, hospital admission less than 24 hours before delivery, principal cause of prematurity (classified as preterm labor, preterm premature rupture of membranes, hypertensive disorders or abruptio placentae, fetal growth retardation, or other [23]), and mode of delivery.

Infant characteristics considered were gestational age at delivery (in completed weeks of gestation), sex, small for gestational age (SGA) using the French intrauterine growth curves,[24] admission temperature (within 12 hours after birth), surfactant (0, 1, or 2 doses) for infants admitted to NICU, and postnatal transfer (including repatriation transfers).

We also investigated 3 evidence-based practices that were recommended in the early 2010s and were identified as improving survival without severe neonatal morbidity in VPT infants [25]: any administration of antenatal corticosteroids before delivery; effective prevention of hypothermia defined as temperature on admission of 36°C or more; and surfactant used within 2 hours or early nasal continuous positive airway pressure (CPAP) for infants born before 28 weeks of gestation for infants admitted to NICU.

This study was approved by the National Data Protection Authority (CNIL no. 911009) and by the appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes - reference no. 10.626, Committee for the Protection of People Participating in Biomedical Research - reference CPP SC-2873).

Table III. Maternal and pregnancy characteristics according to hospital volume

	Hospital volume*				
	<55 (Q1)	55-79 (Q2)	80-109 (Q3)	≥110 (Q4)	
Number (%) of mothers	n = 213 (10.5%)	n = 459 (22.2%)	n = 598 (29.1%)	n = 799 (38.3%)	*P*
Maternal characteristics, n (%)					
Maternal age (y)					.18
<25	44 (20.5)	96 (20.6)	137 (22.7)	132 (16.6)	
25-34	119 (55.8)	265 (57.7)	326 (54.7)	482 (60.2)	
≥35	50 (23.7)	98 (21.7)	135 (22.6)	185 (23.2)	
Mother born outside of France	40 (19.2)	112 (25.1)	112 (21.0)	194 (27.1)	.03
Socioeconomic status					.008
Professional/intermediate	74 (36.0)	168 (39.0)	209 (38.2)	327 (43.9)	
Other	117 (59.1)	237 (54.6)	309 (56.7)	408 (53.8)	
Not employed	19 (4.9)	28 (6.3)	29 (5.1)	17 (2.3)	
Nulliparous women	112 (54.6)	223 (51.7)	285 (51.0)	420 (55.6)	.34
Infertility treatment	21 (9.7)	55 (12.0)	72 (12.4)	136 (17.3)	.001
Doses of antenatal steroids					.0001
0	37 (18.4)	81 (17.8)	78 (13.2)	59 (7.6)	
1	37 (17.8)	61 (14.0)	90 (15.0)	130 (16.5)	
2	128 (63.8)	296 (68.2)	411 (71.8)	584 (75.8)	
Singleton	180 (84.9)	358 (78.1)	484 (80.7)	632 (79.2)	.19
Antenatal transfer	99 (46.8)	213 (48.2)	362 (60.7)	510 (63.7)	.001
Admission less than 24 h before delivery	103 (47.7)	238 (52.2)	310 (51.6)	426 (53.0)	.4
Principal cause of preterm delivery					.8
Preterm labor	80 (36.3)	160 (34.0)	209 (34.1)	295 (36.2)	
PPROM	59 (28.2)	130 (27.7)	155 (25.6)	230 (27.9)	
Hypertensive disorders or placental abruption	53 (25.4)	118 (26.7)	161 (27.7)	181 (23.7)	
Fetal growth retardation	11 (5.5)	31 (7.2)	34 (6.1)	44 (5.9)	
Other circumstances	10 (4.6)	20 (4.4)	39 (6.5)	49 (6.3)	
Cesarean delivery	139 (66.1)	289 (66.0)	406 (69.2)	515 (66.8)	.68

PPROM, preterm premature rupture of membranes.
*Annual number of admissions of newborns under 31 weeks.

Statistical Analyses

Univariate analyses were performed to describe the population characteristics and evidence-based practices according to hospital volume, using χ^2 tests. Statistical significance was set at a 2-tailed test with *P* values of < .05. We used weighted percentages and gestational age adjustments in the multivariable analyses to account for differences in sampling times between gestational age groups.

Multivariate logistic regression analyses with population average models were used to analyze the association between hospital volume and the study outcomes taking into account clinical and healthcare factors known to affect outcomes and

Table IV. Neonatal characteristics according to hospital volume

	Hospital volume*				
	<55 (Q1)	55-79 (Q2)	80-109 (Q3)	≥110 (Q4)	
Number (%) of newborns	n = 243 (10.1%)	n = 552 (22.6%)	n = 700 (28.8%)	n = 952 (38.5%)	*P*
Neonatal characteristics, n (%)					
Gestational age (wk)					.27
24-25	30 (9.8)	75 (10.9)	90 (10.2)	156 (13.3)	
26-27	62 (24.1)	156 (26.4)	192 (25.8)	274 (27.0)	
28-30	151 (66.1)	321 (62.7)	418 (64.0)	522 (59.7)	
Male sex	114 (46.3)	293 (53.6)	389 (55.5)	501 (53.0)	.11
SGA†	91 (38.2)	201 (37.3)	241 (35.5)	313 (33.9)	.47
Admission temperature (°C)					.007
<36	84 (37.3)	173 (31.3)	197 (30.6)	247 (26.0)	
36-37.9	130 (61.3)	352 (67.0)	425 (68.3)	641 (72.0)	
≥38	3 (1.4)	8 (1.6)	7 (1.1)	18 (2.0)	
Doses of surfactant (<28 wk)					.007
0	11 (13.6)	9 (5.0)	19 (8.0)	20 (5.1)	
1	54 (62.6)	145 (67.7)	142 (54.7)	254 (63.8)	
2	20 (23.6)	62 (27.4)	99 (37.3)	126 (31.0)	
Postnatal transfer					.001
0	173 (72.8)	310 (56.7)	388 (56.0)	508 (54.0)	
1	48 (20.7)	158 (30.6)	234 (34.7)	357 (38.9)	
≥2	16 (6.5)	74 (13.2)	65 (9.3)	68 (7.1)	

*Annual number of admissions of newborns under 31 weeks.
†SGA was defined as birth weight <10th percentile for gestational age and sex based on French intrauterine EPOPé curves (EGO et al 2016).

hospital volume. These factors were sex, gestational age, SGA (<10th percentile),[24] maternal age, infertility treatment, principal cause of prematurity, multiple or singleton pregnancy, parental socioeconomic status, and mother's country of birth. We used a generalized estimating equation approach to take into consideration the clustering of births within hospitals.[26]

To check the robustness of the results, 2 sensitivity analyses were performed. First, for children aged between 24 and 25 weeks of gestation, there was no consensus about active management across French regions in 2011,[18,27] and the decision to initiate resuscitation at birth varied greatly between hospitals. These children are considered to be on the edge of viability in France.[28,29] Therefore, we conducted analysis on a restricted population of 26-30 weeks for whom active resuscitation was commonly initiated in France.[30] Second, as mortality is higher in French overseas departments and territories,[31] an analysis was conducted on only the newborns born in metropolitan France. Finally, because newborns were potentially transferred to another level III unit after birth, we performed a sensitivity analysis by excluding newborns hospitalized in more than one level III unit.

Survival at discharge was reported for all live births. In contrast, to account for dropouts and missing information, survival without severe neonatal morbidity at discharge and survival without neuromotor and sensory disability at 2 years of corrected age was reported after multiple imputation. Among survivors, results are reported for both complete cases and all cases after multiple imputation. Missing data were imputed by chained equations using the SAS "MI" procedure.[32] Imputation model variables included maternal, antenatal, and neonatal characteristics (maternal age, parity, parental socioeconomic status, country of birth, infertility treatment, principal cause of prematurity, antenatal steroids, multiple pregnancy, caesarean section, SGA, gestational age, sex, Apgar score, surfactant, admission temperature), and outcomes (severe neonatal morbidities, cerebral palsy, neuromotor or sensory disabilities, and ASQ). For ASQ, missing domains were separately imputed to account for partially completed questionnaires and ASQ score was then estimated using the imputed domain specific data for infants without cerebral palsy, deafness, or blindness. Binary variables were imputed using logistic regression and socioeconomic data were imputed using multinomial models. We generated 50 independent imputed datasets with 30 iterations each. Estimates were pooled according to the Rubin rule.[33] Further details are available in **Table I** (available at www.jpeds.com). All

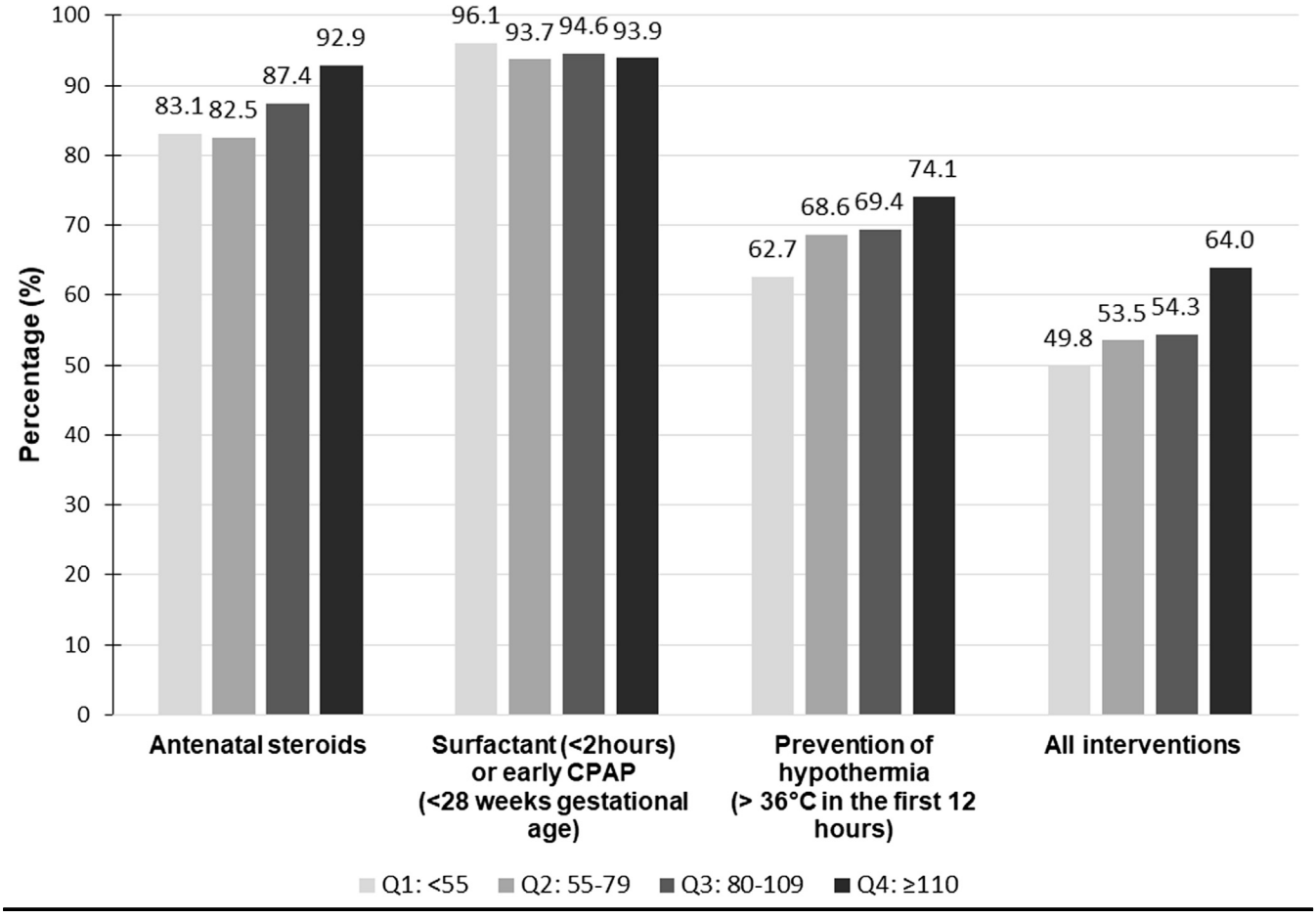

Figure 2. Evidence-based interventions according to hospital volume among infants of 24^{+0} to 30^{+6} weeks of gestation admitted to neonatal care. χ^2 test: $P < .05$ for antenatal steroids, prevention hypothermia, and all 3 interventions.

Table V. Live birth outcomes according to hospital volume, using logistic regression generalized estimating equation model

Outcomes	Method	Hospital volume* <55 (Q1) n = 243	55-79 (Q2) n = 552	80-109 (Q3) n = 700	≥110 (Q4) n = 952
Survival at discharge					
% (95 % CI)	CC	85.7 (81.5-89.9)	88.1 (85.4-90.7)	87.5 (85.2-89.9)	88.6 (86.7-90.5)
aOR [95% CI]†		0.56 [0.33-0.91]	0.90 [0.57-1.43]	0.81 [0.55-1.20]	1
Survival without severe neonatal morbidity					
% (95 % CI)	MI	72.4 (66.5-78.2)	73.8 (69.4-78.3)	65.2 (54.3-76.0)	70.3 (64.7-75.9)
aOR [95% CI]†		0.80 [0.50-1.26]	1.04 [0.70-1.53]	0.71 [0.48-1.03]	1
Survival without neuromotor or sensory disabilities at 2 y of corrected age					
% (95 % CI)	MI	75.0 (54.6-95.3)	76.7 (58.9-94.5)	77.8 (60.1-95.6)	80.7 (67.5-93.9)
aOR [95% CI]†		0.60 [0.38-0.95]	0.79 [0.51-1.21]	0.83 [0.58-1.20]	1

CC, complete (fully documented) cases; *MI*, available cases after multiple imputation.
*Annual number of admissions of newborns under 31 weeks.
†Adjusted for gestational age, sex, SGA, multiple pregnancy, maternal age, infertility treatment, principal cause of prematurity, parental socioeconomic status, and mother's country of birth.

analyses were carried out with SAS v 9.4 software (SAS Institute Inc, Cary, North Carolina).

Results

Admissions per year were <55 (quartile 1, Q1), 55-79 (Q2), 80-109 (Q3), and ≥110 (Q4), with a range of 14 to 174 very preterm babies admitted per hospital. Hospital characteristics are presented in **Table II** (available at www.jpeds.com). Of the high-volume hospitals, 87% were part of a University system and 80% performed neonatal surgery.

In total, 2447 infants were born between 24 and 30 weeks of gestation in 66 level III hospitals (**Figure 1**; available at www.jpeds.com). **Table III** and **Table IV** provide maternal and neonatal characteristics according to hospital volume. Q4 hospitals had higher proportions of women born outside France and of women from a higher socioeconomic status.

Only 10% of newborns were admitted to low volume units (Q1). In this group, significantly fewer women received fertility treatment or were transferred before delivery. Moreover, compared with infants born in Q4 hospitals, infants born in Q1 hospitals less frequently received antenatal steroids or surfactant and presented more frequently with hypothermia. The principle cause of preterm delivery, gestational age, SGA, and sex did not differ according to hospital volume.

The proportion of infants receiving all 3 evidence-based interventions increased significantly with hospital volume, from 49.8% in Q1 hospitals to 64.0% in Q4 hospitals. The proportion of infants receiving surfactant therapy or early nasal CPAP did not significantly differ according to hospital volume (**Figure 2**).

Survival at discharge was lower in Q1 hospitals (aOR 0.56, 95% CI 0.33-0.91, **Table V**). The percentages of severe neonatal morbidity were significantly higher in the 2 top quartiles (**Table VI**; available at www.jpeds.com). Survival without severe neonatal morbidity did not differ with hospital volume (**Table V**).

A total of 2116 infants were discharged home, 13 died after discharge and 104 children did not participate in follow-up. In all, 1999 children were included in follow-up; the medical questionnaire for 2 years of corrected age was completed for 1764 children (83.4%) and the ASQ at 22-26 months of corrected age was available for 1232 (58.6%) (**Figure 1**). Data were more frequently missing from children born to families with low socioeconomic status (**Table I**). Survival without neuromotor or sensory disabilities at 2 years was lower in Q1, Q2, Q3 hospitals vs Q4 hospitals, but the aOR was only significantly lower in Q1 hospitals (aOR 0.60, 95% CI 0.38-0.95) (**Table V**). Results from the sensitivity analyses were similar (**Table VII**; available at www.jpeds.com). Our findings were also similar when we excluded newborns (n = 49) who were hospitalized in several level III units (Data not shown). Among surviving infants, we found no significant difference in the incidence of neuromotor or sensory disabilities or ASQ below threshold according to hospital volume (**Table VIII**; available at www.jpeds.com).

Discussion

In this population-based cohort study, we found that infants born between 24 and 30 weeks of gestation and admitted to low volume neonatal units had consistently lower aOR for survival without neuromotor or sensory disabilities at 2 years of corrected age vs high volume units. Neuromotor and sensory disabilities and low ASQ score did not vary with hospital volume.

The EPIPAGE-2 study is based on a large national prospective cohort. Numerous maternal and neonatal characteristics were collected, thus, increasing the robustness of the adjustments. A robust system of verification was used involving study statisticians and local investigators with access to original care notes. We used the volume of admission of VPT newborns in NICU as the exposure variable because this variable is a more relevant and accurate indicator of medical activity in the management of preterm infants than other

indicators such as obstetric volume. Our exposure variable was based on reliable data from the national hospital discharge database.[34] A generalized estimating equation approach was used to take into consideration the clustering of births within hospitals, and sensitivity analyses were performed to account for possible variations in management of VPT newborns between perinatal networks. Only live births in level III hospitals were included; this selection limits the generalization of our results for all neonates born between 24 and 30 weeks, but it has the advantage of analyzing relatively similar services (staff and equipment) and relatively similar newborns not transferred after birth.

The main limitation of our study is the follow-up rate at 2 years, which was lower than in other recent cohort studies on extremely preterm births,[35-37] but these studies included fewer infants. The proportion of children lost to follow-up was higher in families with low socioeconomic status[19] and in hospitals with low neonatal activity, but the neonatal characteristics of these children were similar to those followed-up. Multiple imputation was used to account for missing data.

The quality of care received by newborns during their successive neonatal hospitalizations until discharge may have affected the relationship between hospital volume in the initial hospital and outcomes even though there were fewer postnatal transfers among children born in low volume hospitals.

If volume is an indicator of the experience and organization of a service, it would be better to use the volume before inclusion (2010), but the collection of gestational age in the national hospital discharge database only became mandatory in 2011. NICU volume may be a surrogate for other hospital characteristics or case-mix that contributes to the risk of disabilities. To limit this effect, children with lethal malformations were excluded, and numerous risk factors were introduced in the models.

In our study, a large proportion of NICUs had a high number of admissions, making it difficult to distinguish effects between NICUs with over 55 admissions of VPT newborns per year. In addition, our sample was not large enough to detect moderate differences in the intermediate groups, which might have clinical significance. We were also unable to identify an admission threshold in the lowest-volume NICUs for which survival without disability would be significantly lower. One previous study[7] used modeling techniques to select the thresholds for investigation, but this required a much larger sample size, and they did not present data on longer-term neurodevelopment.

Another limitation is the lack of data on maternal distance to the closest level III maternity unit. However, low-volume NICUs (Q1) are not always located in isolated areas; for example, only 3 out of the 40 perinatal networks existing in 2011 had a low volume NICU as the sole NICU in the network. In addition, outborn infants are most affected by distance,[38,39] but our study did not include this population.

Previous studies on the effect of volume on neonatal care have mainly used retrospective cohorts,[7,11,12] which had the advantage of large populations, but only studied in-hospital mortality and severe neonatal morbidity. These studies found that hospitalization in the top volume quartile was associated with a decreased risk of death. However, improved survival can potentially lead to an increase in the number of vulnerable infants developing neonatal and long-term complications. We found a trend toward increased severe neonatal morbidity in our study, and 2 other studies have shown an increased risk of bronchopulmonary dysplasia and retinopathy of prematurity treatment in large units.[11,12] Our results suggest, however, that neuromotor and sensory disabilities at 2 years of age and psychomotor development did not differ with neonatal unit volume.

To understand the differences in survival between hospitals, factors such as number of beds, university status, and level of care have been explored, but none were shown to be associated with survival.[9,10] On the contrary, the association with NICU volume found in several countries shows the importance of this factor. A high volume of activity may be associated with other beneficial factors such as better coordination of obstetric-pediatric care, more experienced caregiving staff, or better implementation of clinical guidelines, as our study suggests. The 3 clinical practices investigated in our study can be considered indirect markers of the quality of perinatal care because they have been strongly recommended since 2011 and involve both obstetrical (antenatal steroids) and neonatal practices (prevention of hypothermia and surfactant or early nasal CPAP). The large variability of clinical practices across countries[40,41] suggests that other clinical practices should be considered to understand which practices have a major impact on infant health. Evidence-based practices should be encouraged through appropriate training and evaluation in particular in the smallest volume hospitals. Morbidity and mortality reviews and the clinical pathway, as described by Rotter et al, are methods for evaluating and improving practices and could help obstetrical and neonatal teams improve the management of VPT infants.[42]

Our results suggest that volume has an impact on survival without neuromotor and sensory disabilities mainly in the lowest activity units. This raises the question of whether it is necessary to establish volume thresholds for the admission of very preterm births in neonatal units, as recommended or enforced for level III units since 2003 in Belgium, Germany (50 VLBW), the Netherlands (200 total admissions),[43] and in the United Kingdom (100 VLBW).[44] However, closing the lowest activity NICUs could impede or delay maternal transfers, thereby increasing the number of infants born outside level III hospitals.[39] Policy decisions regarding perinatal regionalization must, therefore, weigh the respective impact of NICU volume and the geographic access to these units, as has been done in limited-access zones.[45]

In conclusion, our study suggests that the higher survival rate in the highest volume neonatal units was not followed by a higher risk of disability at 2 years of age. Further studies should focus on why survival at discharge for very preterm infants admitted to small-volume neonatal units is

significantly lower. Our results add new information to the ongoing debate on the optimal regionalization of perinatal care. ■

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Reprint requests: Thomas Desplanches, RM, MSc, CHRU Dijon, Department of Gynecology, Obstetrics, Fetal Medicine, and Infertility, 4 boulevard de Lattre de Tassigny, 21000 Dijon, France. E-mail: thomas.desplanches@inserm.fr

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50 Years Ago in *The Journal of Pediatrics*

Otitis Media in Children: Incidence, Treatment, and Prognosis in Pediatric Practice

Brownlee RC, DeLoache WR, Cowan CC, Jackson HP. J Pediatr 1969;75:636-42.

An analysis by Brownlee et al of the records of 772 children who experienced 2876 episodes of acute otitis media shed light on a leading reason for physician visits. Myringotomy was found to be indicated only after "intensive and prolonged medical management" failed to clear the condition, and tonsillectomy and adenoidectomy did not significantly influence the later occurrence of otitis media. Most patients were effectively treated with penicillin or tetracyclines. Of note, the investigators recognized recent knowledge of tetracyclines' adverse effects on children. Patients were evaluated for hearing loss by audiometry; 2.3% of patients with otitis media developed hearing loss, compared with 1.6% of patients without otitis media. This led the investigators to conclude that "the incidence of deafness was not shown to bear a significant relationship to otitis media."

Current practice generally calls for myringotomy after "intensive and prolonged medical management" in much the same way as 50 years ago. Similarly, debate remains on the place of other surgical interventions, such as tonsillectomy and adenoidectomy; however, they are recognized as adjuvant procedures in patients with tympanostomy tubes. In regard to complications, it is now accepted that otitis media can result in sensorineural hearing loss.

Fifty years ago, penicillin was considered "an effective and practical method of eradicating this condition"; penicillins continue to be the recommended first-line treatment. Although effective treatments are available, shortcomings remain. Global shifts in antimicrobial susceptibility highlight the importance of vaccination, and the development of novel therapies. Specifically, vaccination against pneumococcus, and influenza provides a measure of protection. Several recent advances offer the potential for improved management, including the discovery of numerous promising vaccine antigens against *Moraxella catarrhalis,*[1] one of the most common pathogens causing otitis media, as well as the identification of mouse genes as relevant candidates for human disease.[2]

Julio C. Ramirez, MD
Department of Pediatrics
Saint Louis University School of Medicine
Cardinal-Glennon Children's Hospital
St. Louis, Missouri

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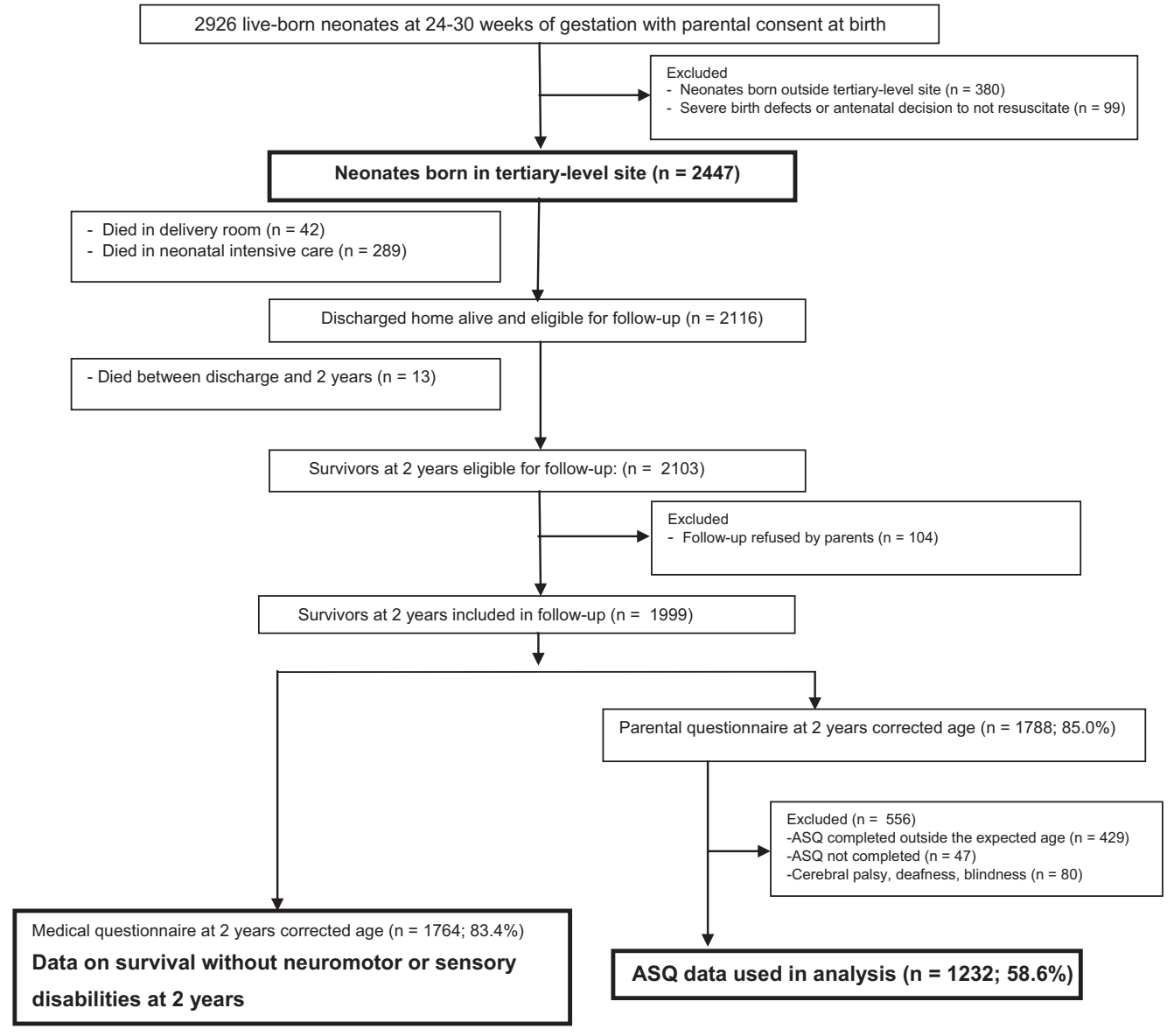

Figure 1. Flow chart of study population.

Table I. Comparison of characteristics among responders and non-responders

Characteristics	Survivors at 2 y corrected age eligible for the study Neuromotor and sensory disabilities data available: Yes n = 1764	Survivors at 2 y corrected age eligible for the study Neuromotor and sensory disabilities data available: No n = 339	*P* value
Maternal characteristics, n (%)			
Maternal age (y)			.0001
<25	274 (15.6)	104 (30.2)	
25-34	1076 (60.9)	163 (48.0)	
≥35	414 (23.5)	72 (21.8)	
Mother born outside of France	364 (22.3)	90 (29.5)	.007
Socioeconomic status			.0001
Professional/intermediate	767 (45.3)	75 (25.7)	
Other	877 (52.0)	202 (66.8)	
Not employed	46 (2.7)	22 (7.4)	
Multiple pregnancy	589 (33.3)	101 (29.4)	.15
Antenatal transfer	989 (56.5)	216 (63.8)	.01
Infertility treatment	339 (19.4)	41 (12.5)	.003
Doses of antenatal steroids			.02
0	183 (10.7)	48 (14.1)	
1	263 (15.4)	35 (10.5)	
2	1259 (73.9)	244 (75.4)	
Principal cause of preterm delivery			.09
Preterm labor	656 (36.5)	114 (33.3)	
PPROM	475 (26.5)	108 (31.1)	
Hypertensive disorders or Placental abruption	413 (24.1)	64 (19.8)	
Fetal growth retardation	105 (6.3)	21 (6.6)	
Other circumstances	115 (6.6)	32 (9.2)	
Cesarean delivery	1210 (70.0)	205 (63.0)	.01
Neonatal characteristics, n (%)			
Gestational age (wk)			.4
24-25	170 (7.6)	36 (8.4)	
26-27	465 (24.5)	85 (23.2)	
28-30	1129 (67.9)	218 (68.5)	
Male sex	946 (53.8)	162 (47.8)	.04
SGA	609 (35.2)	116 (35.4)	.9
Admission temperature (°C)			.76
<36	478 (27.6)	89 (27.1)	
36-37.9	1180 (70.7)	224 (70.6)	
≥38	27 (1.7)	7 (2.3)	
Doses of surfactant (<28 wk)			.10
0	482 (29.3)	110 (35.2)	
1	946 (53.8)	164 (49.6)	
2	305 (16.9)	54 (15.2)	
Severe neonatal morbidities	32 (18.3)	65 (19.5)	.62
Hospital volume, n (%)			.001
<55	157 (9.1)	47 (14.1)	
55-79	395 (22.3)	79 (23.2)	
80-109	485 (27.8)	114 (33.7)	
≥110	727 (40.8)	99 (29.0)	

PROMM, preterm premature rupture of membranes.

Table II. Hospital characteristics according to hospital volume

Hospital characteristics (n = 66)	Hospital volume* <55 n = 17 (26%)	54-79 n = 17 (26%)	80-109 n = 17 (26%)	≥110 n = 15 (23%)
University hospital, n (%)	3 (18.0)	9 (53.0)	12 (70.0)	13 (87.0)
Type of surgery available†, n (%)				
0	10 (58.8)	7 (41.1)	4 (23.5)	3 (20.0)
≥1	7 (41.8)	10 (58.6)	13 (76.5)	12 (80.0)
Number of neonatal resuscitation beds, mean/median	6.2/6.0	9.3/8.0	11.9/12.0	14.6/15.0

*Annual number of admissions of newborns under 31 weeks.
†Ability to perform at least 1 of the following interventions; laparotomy for necrotizing enterocolitis, patent ductus arteriosus ligation, and insertion of ventriculoperitoneal shunt.

Table VI. Association between hospital volume and severe neonatal morbidity

Outcomes	Hospital volume* < 55 n = 243 (10.1%)	55-79 n = 552 (22.6%)	80-109 n = 700 (28.8%)	≥ 110 n = 952 (38.5%)	Total	*P*	Missing data (%)
Severe neonatal morbidity† N = 2116, n/N (%)	32/198 (14.5)	75/463 (14.8)	115/520 (21.2)	151/776 (18.5)	373/1957	.02	7.5
BPD	16/200 (7.0)	47/463 (9.0)	49/528 (8.4)	78/788 (9.2)	190/1979	.74	6.9
cPVL or IVH (III/IV)	13/204 (6.0)	23/480 (4.5)	44/602 (7.1)	45/830 (4.8)	125/2116	.24	0
NEC (II or III)	5/203 (2.1)	8/477 (1.6)	36/588 (6.2)	29/822 (3.6)	78/2090	.003	1.2
ROP	4/202 (1.5)	6/479 (1.0)	7/592 (1.0)	18/824 (1.9)	35/2097	.31	1.0
Crude OR	1.00 [0.63-1.60]	0.89 [0.60-1.33]	1.35 [0.87-2.10]	1			
aOR‡	1.21 [0.72-2.08]	0.93 [0.59-1.45]	1.44 [0.81-2.56]	1			

BPD, bronchopulmonary dysplasia; *cPVL*, cystic periventricular leukomalacia; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *ROP*, retinopathy of prematurity.
Missing data = 159.
*Annual number of admissions of newborns under 31 weeks.
†At least 1 of these diseases: severe BPD; IVH, severe IVH, cPVL, NEC, or ROP.
‡Adjusted for gestational age, sex, SGA, multiple pregnancy, maternal age, infertility treatment, principal cause of prematurity, parental socioeconomic status, and mother's country of birth.

Table VII. Sensitivity analysis

Outcomes	Method	Hospital volume* <55 (Q1)	55-79 (Q2)	80-109 (Q3)	≥ 110 (Q4)	Total
Survival without neuromotor or sensory disabilities at 2 y corrected age in infants born between 26 and 30 weeks of gestation						
N		213	477	610	796	2096
% (95 % CI)	MI	77.9 (60.9-94.9)	80.2 (67.2-93.0)	82.3 (70.7-93.9)	85.1 (75.9-94.2)	
aOR [95% CI]†	MI	0.57 [0.36-0.90]	0.69 [0.44-1.07]	0.80 [0.55-1.16]	1	
Survival without neuromotor or sensory disabilities at 2 y of corrected age in metropolitan France						
N		216	493	613	952	2274
% (95 % CI)	MI	75.0 (54.6.6-95.3)	76.7 (58.9-94.5)	77.9 (60.2-95.6)	80.7 (67.5-93.8)	
aOR [95% CI]†	MI	0.59 [0.37-0.96]	0.78 [0.49-1.24]	0.87 [0.59-1.27]	1	

MI, available cases after multiple imputations.
*Annual number of admissions of newborns under 31 weeks.
†Adjusted for gestational age, sex, SGA, multiple pregnancy, maternal age, infertility treatment, principal cause of prematurity, parental socioeconomic status, and mother's country of birth.

Table VIII. Survivor outcomes at 2 years corrected age according to hospital volume, using logistic regression generalized estimating equation model

		Hospital volume*			
		<55 (Q1)	55-79 (Q2)	80-109 (Q3)	≥ 110 (Q4)
Outcomes	Method	n = 204	n = 474	n = 599	n = 826
Neuromotor and sensory disabilities					
% (95 % CI)	CC	4.2 (1.0-7.5)	4.8 (2.6-7.0)	3.1 (1.5-4.7)	3.0 (1.7-4.3)
aOR [95% CI]†		1.56 [0.58-4.20]	1.81 [0.87-3.79]	1.06 [0.55-2.03]	1
% (95 % CI)	MI	4.6 (1.3-7.9)	5.2 (2.8-7.5)	3.3 (1.7-5.0)	3.3 (1.9-4.7)
aOR [95% CI]†		1.48 [0.56-3.93]	1.73 [0.85-3.57]	1.05 [0.56-1.97]	1
ASQ score below threshold at 2 y‡					
% (95 % CI)	CC	46.5 (37.2-55.9)	44.7 (38.7-50.8)	43.5 (38.0-48.3)	40.6 (36.3-44.9)
aOR [95% CI]†		1.39 [0.82-2.37]	1.06 [0.75-1.50]	0.97 [0.72-1.32]	1
% (95 % CI)	MI	49.9 (41.4-58.4)	49.6 (44.2-55.0)	47.4 (42.7-52.1)	45.9 (41.9-49.9)
aOR [95% CI]†		1.37 [0.88-2.14]	1.00 [0.70-1.42]	0.99 [0.74-1.33]	1

CC, complete (fully documented) cases.
*Annual number of admissions of newborns under 31 weeks.
†Adjusted for gestational age, sex, SGA, multiple pregnancy, maternal age, infertility treatment, principal cause of prematurity, parental socioeconomic status, and mother's country of birth.
‡Infants with cerebral palsy, deafness, or blindness were excluded.