Use of evidence-based practices to improve survival without severe morbidity for very preterm infants: results from the EPICE population-based cohort

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What is already known

1. Very preterm infants face high risks of mortality and severe neonatal morbidity compared to term infants
2. Effective perinatal interventions exist to improve survival and reduce neonatal morbidity.
3. Country and unit variations in very preterm outcome are large and may reflect sub-optimal use of evidence-based care.

What this paper adds

1. Only 58.3% of very preterm infants admitted for neonatal care in 19 European regions received all of 4 evidence-based practices for which they were eligible.
2. These very preterm infants had higher risk-adjusted survival without severe morbidity, suggesting more comprehensive provision of evidence-based practices could yield substantial gains.
3. Our findings support the growing focus on bundling effective practices to improve processes of care and to achieve best outcomes.

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All authors have completed the Unified Competing Interest form atwww.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency

The lead author, Jennifer Zeitlin, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. This manuscript provides ethics, funding and STROBE checklist for observational studies

- Details of ethical approval (in the manuscript)
- Details of funding (in funding statement in acknowledgements)
- Statement of independence of researchers from funders (in funding statement in acknowledgements)
- STROBE Checklist (as supplementary material)

Author Contributions

JZ and RFM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They act as guarantors of the study.

Study concept and design: JZ, BM, MC, EB, AvH, JG, LH, TW, SS, PVR, HB, DD, LT, MN, BB, MB, ESD, RFM; Acquisition, analysis, or interpretation of data: JZ, BM, AP, MC, EB, AvH, JG, LH, TW, SS, PVR, HB, DD, LT, MN, BB, MB, ESD, RFM and all authors in Epice Research Group; Drafting of the manuscript: JZ, BM, AP, MC, EB, AvH, JG, LH, TW, SS, PVR, HB, DD, LT, MN, BB, MB, ESD, RFM; Critical revision of the manuscript for important intellectual content and approval of final version of the manuscript: All authors (including authors listed in EPICE Research Group); Statistical analysis: JZ, BM, AP, MB; Study supervision: JZ, BM, ESD; Obtained funding: GM, OP, LT, JZ, RFM,MC, DD, AvH, JG, HB, MN, ESD

Data sharing:

Statistical code is available from the corresponding author. No additional data are available.

Acknowledgements

We are thankful to Elizabeth Howell, Michael Obladen, Raphael Porcher and Philippe Ravaud for their input on draft versions of this manuscript. Permission was requested for these acknowledgements.

We would like to acknowledge the participation of the Departments of Obstetrics and Neonatology from hospitals in the EPICE regions (listed in supplementary acknowledgements' file).

Funding statements

The research leading to these results received funding from the European Union's Seventh Framework Programme ([FP7/2007-2013]) under grant agreement n°259882.

Additional funding is acknowledge from the following regions: **France** (French Institute of Public Health Research/Institute of Public Health and its partners the French Health Ministry, the National Institute of Health and Medical Research, the National Institute of Cancer, and the National Solidarity Fund for Autonomy; grant ANR-11-EQPX-0038 from the National Research Agency through the French Equipex Program of Investments in the Future; and the PremUp Foundation); **Poland** (2012-2015 allocation of funds for international projects from the Polish Ministry of Science and Higher Education); **Sweden** (Stockholm County Council (ALF-project and Clinical Research Appointment) and by the Department of Neonatal Medicine, Karolinska University Hospital), and by the Department of Neonatal Medicine, Karolinska University Hospital); **UK** (funding for The Neonatal Survey from Neonatal Networks for East Midlands and Yorkshire & Humber regions).

The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Abstract

Objectives –To evaluate the implementation of four high-evidence practices for the care of very preterm infants in order to assess their use and impact in routine clinical practice and whether they constitute a lever for reducing mortality and neonatal morbidity.

Design – Prospective multi-national population-based observational study of infants born before 32 weeks of gestational age.

Setting – 19 regions from 11 European countries covering 850,000 annual births participating in the EPICE (Effective Perinatal Intensive Care in Europe for very preterm births) project.

Participants – Infants born between 24+0 and 31+6 weeks gestational age without serious congenital anomalies and surviving to neonatal admission (N=7,336) in 2011/2012.

Main outcome measures - Combined use of four evidence-based practices using an All-or-None approach: delivery in a maternity unit with appropriate level of neonatal care; administration of antenatal corticosteroids; hypothermia prevention (neonatal unit admission temperature of ≥36 °C); surfactant within 2 hours of birth or early nasal continuous positive airway pressure for infants born before 28 weeks gestational age. Infant outcomes were in-hospital mortality, severe neonatal morbidity at discharge and a composite measure of death and/or severe morbidity. We modelled associations using risk ratios (RR) with propensity score weighting to account for potential confounding bias. Analyses were adjusted for clustering within delivery hospital.

Results: Only 58.3% of infants received all evidence-based practices for which they were eligible. Infants with low gestational age, growth restriction, low Apgar scores and born on the day of maternal admission to hospital were less likely to receive evidence-based care. After adjustment, evidence-based care was associated with lower in-hospital mortality (RR=0.72, 95% confidence interval 0.60 to 0.87) and in-hospital mortality or severe morbidity (RR=0.82, 95% confidence interval 0.73 to 0.92), corresponding to an estimated 18% decrease in all deaths without an increase in severe morbidity if these interventions had been provided to all infants.

Conclusions: More comprehensive use of evidence-based practices in perinatal medicine could result in significant gains for very preterm infants, in terms of increased survival without severe morbidity.

Words: 328

Introduction

Very preterm infants, born before 32 weeks of gestational age , represent fewer than two percent of all births, but up to half of infant deaths.[1] For survivors, risks of cerebral palsy, visual and auditory deficits, cognitive impairments, psychiatric disorders and behavioural problems are much higher than for children born at term.[2] Ensuring the best outcomes for very preterm infants is essential for their future health and development and for reducing the burden associated with very preterm delivery for families and healthcare and social systems.

The existence of wide disparities in the risk-adjusted mortality and morbidity of very preterm infants across countries and neonatal units suggests that substantial gains are possible using current medical knowledge.[3-7] Research comparing the care of very preterm infants across countries and units supports this assertion, as practices are not always consistent with the latest scientific evidence, including non-use of treatments shown to be effective and safe and use of others for which evidence is limited or where safety is of concern.[8-13]

The promotion of applied evidence-based care may thus be an important lever for achieving better outcomes in this high risk population, as shown in other areas of medicine.[14-17] Research from many medical specialties has highlighted the challenges of translating even very convincing scientific knowledge into practice because of organisational, cultural or personal barriers.[18-20] Moreover, while evidence-based interventions are shown to be effective in clinical trials, the selection criteria applied to achieve equipoise and ensure rigorous implementation of the protocol may limit the generalizability of results to the overall population of patients. It is thus necessary to produce knowledge on the use of interventions by clinicians and health planners and their impact in unselected populations.

The EPICE (Effective Perinatal Intensive Care in Europe) project established a population-based cohort of very preterm infants in 19 regions in 11 European countries to investigate the use of

evidence-based practices and their association with outcomes in real-life clinical settings. In this study, we investigate the use of four practices which have a high-level of evidence for the care of very preterm infants and measure their association with mortality and/or neonatal morbidity.

Methods

Study design

The EPICE cohort is a geographically defined prospective study of all very preterm stillbirths and live births from 22+0 weeks to 31+6 weeks of gestation born in all public and private maternity hospitals, in 19 regions in 11 European countries covering over 850,000 births annually: Belgium (Flanders); Denmark (Eastern Region); Estonia (entire country); France (Burgundy, Ile-de-France and the Northern region); Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio and Marche); the Netherlands (Central and Eastern region), Poland (Wielkopolska); Portugal (Lisbon and Northern region); Sweden (greater Stockholm) and the United Kingdom (East Midlands, Northern, and Yorkshire & Humber regions). Regions were selected with respect to geographic and organisational diversity, feasibility (on-site infrastructure and expertise for implementing the protocol), and sample size considerations. Data were collected between April 2011 and September 2012; in each region inclusions occurred over 12 months, except in France (6 months).

Investigators abstracted data from medical records in obstetrical and neonatal units using a pretested standardised questionnaire with common definitions. Gestational age was defined as the best obstetric assessment based on information on last menstrual period and antenatal ultrasounds, which are part of routine obstetrical care in all regions. When there were several estimates, the following hierarchy was used to determine gestational age for the study: IVF treatment, ultrasound based on earliest estimate, last menstrual period, fundal height measurement, and neonatal assessment at birth. Inclusions were cross-checked against delivery ward registers or another

external data source. Infants were followed up until discharge home from hospital or into long-term care or death.

Ethics approval was obtained in each region from regional and/or hospital ethics committees, as required by national legislation. The European study was also approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL).

Patient involvement

The EPICE study included a European parent organisation in stakeholder meetings about the project's preliminary results and analyses, including this study. EPICE maintains contact with parents in the cohort through regional newsletters and letters and its website. A European parent organisation is part of our consortium for follow-up studies of the cohort.

Study population

The study population comprised all infants without severe congenital anomalies born at 24+0 to 31+6 weeks gestational age and admitted to a neonatal unit (N=7,336 infants delivered in 335 maternity units and admitted to 242 neonatal units). We excluded births before 24 weeks of gestation because there is no consensus across the regions about active treatment for these births[21] (N=301 live births). Infants with severe congenital anomalies were excluded because of regional differences in screening and termination policies[22] (N=126). We also excluded labour ward deaths (N=112 ≥24 weeks) because the EPICE database does not contain information on the degree of emergency in these cases, condition at birth or on neonatal resuscitation practices and we were concerned that these cases were often situations where there was no opportunity to provide evidence-based care. Furthermore, we surmised that reverse causality could be present, i.e. a

decision against active management could explain non-implementation of evidence-based practices. Finally, we excluded out-of-hospital births that were unlikely to receive evidence-based care (N=26).

Definition of evidence-based care: using an All-or-None approach

We used an All-or-None approach to study the use of evidence-based practices. In contrast with an item-by-item assessment of performance or the creation of a composite measure, this approach considers whether all measures have been provided to each eligible patient.[23] A restrained set of indicators is selected which should measure performance on the specified elements of good care and be related to the desired outcomes.[23] The EPICE protocol included 17 practices with varying levels of evidence from which we identified four with a high-level of evidence that are related to neonatal mortality and morbidity and that could be measured reliably using information from medical records as shown in Table S1. Some evidence-based practices included in EPICE were not retained because they are evaluated with respect to longer term outcomes as, for instance, screening for retinopathy of prematurity. Others were not selected because the evidence is not of highest quality and therefore unlikely to be consensually adopted in all regions, such as active management of patent ductus arteriosus.[24] We then established minimum thresholds for evidence-based care which would be accepted across all regions.

Selected indicators were: delivery in a maternity unit with appropriate neonatal care services[25] using national level of care designations (Table S2), any administration of antenatal corticosteroids before delivery,[26] effective hypothermia prevention, defined as an admission temperature of ≥36°C which corresponds to the lower limit of current recommendations[27 28] and surfactant within two hours after birth or early nasal continuous positive airway pressure for infants born before 28 weeks of gestational age.[29 30] We computed a variable measuring the receipt of all practices given each infant's eligibility.

Outcomes

Our outcomes were (i) in-hospital mortality, defined as death before discharge home or into long term paediatric care; (ii) severe neonatal morbidity among infants discharged alive; (iii) in-hospital mortality and/or severe neonatal morbidity. Severe neonatal morbidity comprised intraventricular haemorrhage grade III or IV, cystic periventricular leukomalacia , retinopathy of prematurity stages III to V, and severe necrotizing enterocolitis . Intraventricular haemorrhage grades were determined using Papile's classification[31] and periventricular leukomalacia was recorded only if cystic abnormalities were present on ultrasound or MRI scan. Severe necrotizing enterocolitis was assessed by surgery or peritoneal drainage because Bell stages were not routinely recorded in all regions. We did not include bronchopulmonary dysplasia because large regional variability in respiratory management and oxygen saturation targets affect rates of this outcome variable.[32]

Covariables

We identified clinical and healthcare factors likely to influence both the probability of receiving evidence-based care and our outcomes based on the scientific literature and biological plausibility. These factors included gestational age, sex, multiple pregnancy, pregnancy complications (preterm premature rupture of membranes), eclampsia/preeclampsia and Hemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) syndrome), small for gestational age , type of delivery (prelabour caesarean section, intrapartum caesarean section, vaginal delivery) and 5-minute Apgar score. Small for gestational age was categorised as $<3^{rd}$ and $<10^{th}$ percentiles for gestational age and sex using Hadlock's references adapted to national population values using Gardosi's model.[33] We also identified cases where the birth was more likely to have been unexpected with a rapid onset precluding use of evidence-based practices, defined by delivery on the same day as maternal admission to hospital without in utero transfer. We also assessed neonatal transport in the first 48 hours after delivery (meaning the infant was outborn in the neonatal unit where he or she received care); this variable was not included in multivariable models, but used for sensitivity analyses to

identify infants who were inborn. Other possible confounders were identified for the propensity score analysis (see below).

Missing data

Most variables had low proportions of missing data: <1% (gestational age, birthweight, sex, multiple pregnancy, outborn, antenatal corticosteroids); 1-3% (pregnancy complications, mode of delivery, neonatal morbidity); 4-5% (Apgar score and admission to delivery time). In contrast, admission temperature was missing in 12.1% of cases (N=886). We used multiple imputations chained equations (MICE) to impute missing data, based on all variables in the study.[34] We used 100 imputed datasets.[35] Outcomes were not imputed. Results are presented using the imputed data; however, models using list-wise deletion are included as supplementary tables.

Analysis strategy

We described the use of each evidence-based practice and investigated the factors associated with our All-or-None composite (full evidence-based care). We then investigated the association of full evidence-based care with our three primary outcome variables. For both analyses, we used generalised linear models to take into consideration the clustering of births within hospitals assuming a Poisson distribution with robust standard errors in order to estimate risk ratios (RR).[36] Region was included as a fixed effect.

To assess the impact of use of evidence-based care on outcomes, we developed propensity scores to control for observed confounding factors. Probabilities of receiving full evidence-based care were generated using logistic regression models including investigator-selected covariables (above) and other possible confounders (24 variables in total and 4 interactions, Table S3). Missing values for these additional variables were included as a separate category. We assessed the balance in our co-variables between infants receiving and not receiving evidence-based care after consideration of the propensity score using standardised differences. The propensity score was included in our primary

analyses by weighting each infant by the inverse propensity of his or her group.[37] We compared results from propensity score models to those from a multivariable model adjusting for investigator-selected covariables. We ran our models for all infants and inborn infants born the day after maternal admission to hospital.

To check that our findings did not reflect the influence of only one of the evidence-based practices, we reran our models four times, removing each indicator in turn. We also assessed the impact of non-receipt of one versus 2 or 3 or 4 practices, compared with receiving all interventions, using the multivariable model with investigator-selected covariables. To estimate the impact of receipt of evidence-based care, we predicted cases of death and severe morbidity if all infants and almost all infants received the evidence-based practices for which they were eligible by keeping coefficients and variables values constant and setting the evidence-based care variable to "yes" for all infants or "yes" for 90% of the infants. The 10% of infants assigned to continued non-evidence-based care in the latter model were those with the lowest propensity scores, reflecting their likelihood of receiving evidence-based care based on their characteristics.

Analyses were carried out using STATA 13.0 SE (Stata Corporation, College Station, Texas).

Results

Mean gestational age in our sample was 28.7 weeks, with a mean birthweight of 1,224 grams (Table 1); 24.9% of births were preceded by preterm premature rupture of membranes and 42.7% were prelabour caesarean sections; 23.2% were born on the same day as maternal admission to hospital without in utero transfer; 11.0% were outborn. In-hospital mortality was 9.2% and 10.3% of survivors had a severe neonatal morbidity.

Most infants received at least one of the evidence-based practices (Figure 1): 88.2% for appropriate place of birth, 89.1% for antenatal steroids, 74.3% for an admission temperature of 36°C or more and 83.0% for surfactant within 2 hours or early nasal continuous positive airway pressure. However, only

58.3% of infants received all four practices and 9.6% did not receive at least two of the practices. The probability of receiving full evidence-based care was lower for infants less than 26 weeks gestational age, singletons, small for gestational age infants, infants with low Apgar scores (< 7 at 5 min), transported after birth, and born on same day as maternal admission (Table 2). Full evidence-based care by region ranged from 32.0% to 75.5% and differences remained significant after adjustment for clinical and delivery characteristics.

Mortality and severe morbidity were lower for infants with full evidence-based care in unadjusted comparisons (Table 3). We generated propensity scores ranging from 2% to 97% which achieved balance in our covariables (Table S3). The area under the receiver operating characteristic curve for the propensity score model was 0.76 (95% conficence intervals, 0.75 to 0.77). In propensity score weighted models, mortality was 28% lower for infants receiving all evidence-based practices (RR=0.72, 95% CI: 0.60 to 0.87) and mortality or severe morbidity was 17% lower (RR=0.82, 95% confidence intervals, 0.73 to 0.92). Results were similar in models adjusting for investigator selected covariables and when the analysis was restricted to inborn infants delivered the day after maternal admission to hospital. Sensitivity analyses with different combinations of the evidence-based practices confirmed that one indicator was not driving these associations and using list-wise deletion of missing data yielded similar results (Table S4 and Figure S1).

We also analysed whether there was a dose-response effect whereby infants receiving fewer evidence-based practices had worse outcomes. In adjusted models, compared to infants receiving all evidence-based practices, receiving 1 fewer practice was associated with a RR of mortality of 1.32 (95% confidence intervals, 1.09 to 1.60), having 2 fewer with a RR of 1.55 (95% confidence intervals, 1.23 to 1.95) and 3 or 4 fewer with a RR of 1.81 (95% confidence intervals, 1.26 to 2.61). These estimates for either death and/or severe neonatal morbidity were: 1.20 (95% confidence intervals,1.10 to 1.34), 1.32 (95% CI: 1.12 to 1.44) and 1.59 (95% confidence intervals, 1.30 to 1.94)

respectively. However, most infants not receiving evidence-based care received only one fewer practice (77.0%).

Table 4 illustrates the potential impact of providing evidence-based care more broadly. We simulated two different situations: one where evidence-based care was provided to all eligible infants and one where this care was provided to 90% of eligible infants. The model with evidence-based care provided to all infants predicted a reduction of 28.1% of the 432 deaths in the group that did not receive evidence-based care, which represents a reduction of 17.9% of all deaths. Of the 781 cases of death and/or severe morbidity in the non-evidence-based group, the reduction was estimated at 19.4%, corresponding to 11.3 % of the total 1,341 cases. In the scenario where 90% of infants received full evidence-based care, 18.3% of deaths in the non-evidence-based group would be prevented, representing 11.8% of all deaths. The percentages for mortality and/or severe morbidity were 12.1% and 7.0%, respectively.

Discussion

Principal findings

Only 58.3% of very preterm infants admitted to neonatal care received all evidence-based practices for which they were eligible in our All-or-None measure. In-hospital mortality as well as a combined outcome of mortality and/or severe neonatal morbidity were lower for infants who received all evidence-based care components. These results suggest that more comprehensive use of these high-evidence and widely accessible practices could yield substantial gains in survival without severe morbidity for these high-risk infants.

Strengths and limitations of the study

The strengths of our study are its large and heterogeneous multiregional population-based sample, including public and private health care facilities, which ensures the generalizability of our results to a wide range of settings. The EPICE study also developed common study instruments and protocols to obtain comparable high-quality data across regions. Our study also has limitations. It was challenging to define evidence-based practices which were adapted to diverse cultural and organisational settings and could be identified from data systematically available in medical records; we thus selected the "lowest common denominator" in order to ensure high acceptability of our thresholds in all contexts. Others may prefer more stringent thresholds, for instance, higher admission temperatures or administration of full courses of antenatal steroids. While choosing conservative cut-offs overestimates the use of evidence-based care, it does not invalidate our main finding of low use of these practices and the gains associated with the improvement in evidence-based perinatal management. We excluded labour ward deaths because these cases were more likely to be emergency situations where there was no opportunity to arrange a maternal transfer or administer antenatal steroids and also because of concerns with reverse causality. However, sub-optimal use of evidence-based care probably contributes to the risks of labour-ward death, leading us to underestimate total effects; future studies with data on exact timing of maternal arrival at the hospital, resuscitation practices in the delivery room and parental opinions are needed to explore this question further. We had some missing data on interventions and, in particular, on admission temperature. These cases may reflect less focus on hypothermia prevention and have led to an overestimation of evidence-based care and an underestimation of the impact on outcomes. Finally, our study only included short-term neonatal outcomes; the longer term impacts on child neurodevelopment and other measures of child and family wellbeing are an important area for further investigation.

Comparison with other studies

An All-or-None approach makes it possible to evaluate the process of care and the potential for improvement for high-evidence interventions that are already widely used. We identified four interventions for the care of very preterm infants which are supported by evidence, linked to better health outcomes and could be measured in our study in a standardised way. Two of these refer to the management of the pregnant woman with threatened preterm delivery and two to the early management of the infant. This selection reflects our conviction that optimal outcomes for very preterm infants require both prenatal and postnatal interventions.

Our All-or-None composite comprises practices that all been shown to improve outcome in meta-analyses of randomised controlled trials or observational studies and have been accepted as standard care for over a decade. For the first practice, delivery in an appropriate maternity unit, meta-analyses of observational studies have shown that birth in a maternity unit with on-site neonatal intensive care (often termed a level 3 unit) is associated with better outcomes for very preterm infants.[25] As the specialization of units by level of care differs in Europe,[38] we used regional guidelines to identify appropriate units. For the second practice, administration of antenatal corticosteroids, meta-analyses have shown reductions in neonatal death, respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, and systemic infections.[26] Our third practice focused on hypothermia at admission to the neonatal unit which is associated with higher mortality and morbidity.[28 39] Plastic wraps or bags, plastic caps, skin-to skin-contact, and transwarmer mattresses have all been shown to be effective for the prevention of hypothermia.[40] As the combination of these measures can vary between units, we considered a non-hypothermic temperature at neonatal admission to indicate use of effective evidence-based practices. Multiple definitions of hypothermia are used (below 36.0°C or 36.5C°);[27 28] to ensure consensus on our thresholds, we used the more liberal definition of 36.0°C. Our last practice focused on respiratory management for extremely preterm infants and is based on two recent meta-analyses. One demonstrated less chronic lung disease or death when using early stabilization on nasal continuous positive airway pressure with selective surfactant administration to infants requiring intubation.[30]

The other showed less acute and chronic pulmonary injury and neonatal mortality from surfactant administered within the first 2 hours of life in infants intubated for respiratory distress.[29] Given these results, we judged either early surfactant or early nasal continuous positive airway pressure in infants below 28 weeks of gestation to be evidence-based interventions. This combined criterion is in accordance with European consensus statements.[41 42]

We found high rates of use of each practice – between 75 and 90%, corroborating network and single country studies.[43 44] However, the population receiving full evidence-based care was much lower: fewer than 60% of infants, revealing more severe deficits in the care process. We further illustrated the high population health impact of implementing all these practices by simulating situations in which all and almost all infants received the evidence-based practices for which they were eligible. While we observed a dose-response association related to the number of practices not administered, most infants received only one fewer than the total. These findings underscore the limits of evaluating practices in isolation and support the growing focus in other clinical areas of medicine and other specialities, including adult care, on bundling effective practices to improve processes of care and to achieve best outcomes.[45 46]

While it seems surprising that such a low proportion of infants received these key elements of care, our results corroborate research from many disciplines showing the difficulty of translating effective interventions into routine clinical practice. Barriers include physician education, knowledge and attitudes[20] and organisational obstacles within the unit, such as lack of strong leadership, absence of written protocols, absence of in-service training, no management support and the size of the facility.[47 48] Differences in ethical attitudes influencing active management of extremely preterm infants may be another contributing factor,[21] although the exclusion of births under 24 weeks and labour ward deaths probably minimised this effect. Many countries recommend active management starting at 24 weeks of gestation, but in others this remains a grey zone in which active management

decisions are discussed with parents. [49] Finally, the regulatory context may be one driver of implementation for these interventions, although the relationship between the existence of guidelines and practice is complex.[18 20] All these factors likely contribute to the variability in evidence-based care observed between the European regions included in this study, corroborating previous reports of wide practice variability for the care of very preterm infants across countries and across hospitals within countries.[8 10-12 50]

Our results also showed that the organisational challenges of managing unexpected deliveries contributed to low use of evidence-based care for very preterm infants, although this did not explain the shortfall in use of evidence-based care which existed even for inborn babies whose mothers were hospitalised for at least one day before their birth. Further investigation is needed to assess whether there is an incompressible group of infants for whom provision of the All-or-None composite would not be possible or whether targeted actions, including those related to the organisation of care for women at risk of very preterm delivery, could achieve rates close to 100%.

Conclusion and policy implications

Only 58.3% of very preterm infants admitted for perinatal care in 19 European regions received all of four evidence-based practices for which they were eligible; receipt of evidence-based care was associated with improved survival after taking into consideration clinical and delivery factors which may affect access to care and outcomes. Maximizing the number of very preterm infants who receive the complete set of these well-proven practices could yield substantial gains in survival without increasing severe neonatal morbidity in survivors.

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Table 1 - Clinical characteristics and care of very preterm infants admitted for neonatal care

Indicator		Neonatal admissions (N=7336)
Gestational age (weeks), mean (standard deviation)		28.7 (2.1)
Birthweight (grams), mean (standard deviation)		1224.0 (383.9)
		N (%)
Gestational age	24-26 weeks	1372 (18.7)
	27-29 weeks	2652 (36.2)
	30-31 weeks	3312 (45.1)
Male		3957 (53.9)
Multiples		2300 (31.4)
Small for gestational age[1]		2423 (32.4)
Preeclampsia/Eclampsia/HELLP		1132 (15.7)
Preterm premature rupture of membranes		1791 (25.0)
Prelabour caesarean section		3082 (42.7)
Intrapartum caesarean section		1843 (25.5)
Vaginal delivery		2298 (31.9)
Apgar <7 at 5 minutes		1162 (17.0)
Organisation of delivery		
In utero transfer (IUT)		2147 (29.7)
Delivery on day of maternal admission, no IUT		1605 (23.2)
Neonatal transport in first 48 hours		804 (11.0)
Mortality/Morbidity		
In-hospital mortality		672 (9.2)
Any severe morbidity (survivors to discharge)		669 (10.3)
Intraventricular haemorrhage grade III/IV or cystic Periventricular leukomalacia		407 (6.2)
Retinopathy of prematurity grade III-V		234 (3.6)
Necrotising enterocolitis with surgery		116 (1.8)
Death or severe morbidity		1341 (18.8)
Infants included per region		
Belgium: Flanders		712 (9.7)
Denmark: Eastern		324 (4.4)
Estonia		150 (2.0)
France: Northern		293 (4.0)
France: Burgundy		89 (1.2)
France: Ile-de-France		816 (11.1)
Germany: Hesse		555 (7.6)
Germany: Saarland		132 (1.8)
Italy: Lazio		536 (7.3)
Italy: Emilia		419 (5.7)
Italy: Marche		101 (1.4)
Netherlands: East-Central		368 (5.0)
Poland: Wielkopolska		259 (3.5)
Portugal: Northern		274 (3.7)
Portugal: Lisbon		424 (5.8)
United Kingdom: Northern		406 (5.5)
United Kingdom: East Midlands		545 (7.4)

United Kingdom : Yorkshire & Humber	691 (9.4)
Sweden: Stockholm	242 (3.3)

NOTES 1. Birthweight less than the 10th percentile of intrauterine references

Legend for Figure 1

Receipt of each individual evidence-based intervention in the All-or-None composite as well as receipt of all interventions among infants 24+0 to 31+6 weeks gestation admitted to neonatal care.

Table 2 – Use of four evidence-based (EB) practices by clinical and care characteristics

Characteristics	All evidence-based practices %	Crude Risk Ratio (95% Confidence Interval)	Adjusted Risk Ratio (95% Confidence Interval)
Gestational age			
24-26 weeks	39.2	0.62 (0.55 to 0.70)	0.62 (0.55 to 0.69)
27-29 weeks	61.3	0.97 (0.93 to 1.02)	0.96 (0.92 to 1.01)
30-31 weeks	63.8	Reference	Reference
Sex			
Male	58.7	1.01 (0.98 to 1.05)	1.01 (0.97 to 1.05)
Female	57.8	Reference	Reference
Type of pregnancy			
Singleton	55.7	Reference	Reference
Multiple	63.9	1.17 (1.11 to 1.22)	1.13 (1.08 to 1.18)
Small for gestational age			
<3rd	53.5	0.90 (0.84 to 0.97)	0.88 (0.82 to 0.94)
3- <10th	57.5	0.96 (0.90 to 1.02)	0.92 (0.87 to 0.97)
≥10th	59.9	Reference	Reference
Preterm premature rupture of membranes	67.7	1.23 (1.17 to 1.29)	1.13 (1.08 to 1.19)
Preeclampsia/Eclampsia/HELLP	53.7	0.91(0.84 to 0.99)	0.94 (0.87 to 1.01)
Type of delivery			
Prelabour caesarean section	57.8	1.05 (0.98 to 1.12)	1.04 (0.98 to 1.10)
Intrapartum caesarean section	61.6	1.09 (1.02 to 1.16)	1.03 (0.97 to 1.10)
Vaginal delivery	56.3	Ref	Ref
Apgar score at 5 minutes			
<7	48.9	0.79 (0.74 to 0.85)	0.89 (0.84 to 0.95)
≥7	60.2	Reference	Reference
Delivery			
> 1 day of maternal admission	63.2	1.60 (1.47 to 1.75)	1.59 (1.46 to 1.73)
same day as maternal admission	42.2	Reference	Reference
Regions[2]			
Belgium: Flanders	59.0	1.04 (0.87 to 1.24)	0.99 (0.85 to 1.15)
Denmark: Eastern	49.6	0.87 (0.55 to 1.38)	0.88 (0.55 to 1.41)
Estonia	75.4	1.32 (1.06 to 1.64)	1.36 (1.14 to 1.62)
France: Northern	46.4	0.81 (0.63 to 1.06)	0.82 (0.63 to 1.05)
France: Burgundy	68.5	1.20 (0.85 to 1.69)	1.14 0.88 to 1.48)
France: Ile-de-France	48.4	0.85 (0.73 to 0.99)	0.84 (0.73 to 0.96)
Germany: Hesse	73.4	1.29 (1.16 to 1.43)	1.27(1.15 to 1.39)
Germany: Saarland	62.7	1.10 (0.87 to 1.39)	1.09 (0.86 to 1.38)
Italy: Lazio	42.4	0.75 (0.57 to 0.98)	0.72 (0.55 to 0.95)
Italy: Emilia	67.9	1.19 (1.08 to 1.32)	1.18 (1.08 to 1.29)
Italy: Marche	51.5	0.90 (0.76 to 1.07)	0.93 (0.78 to 1.11)

Netherlands: East-Central	49.2	0.86 (0.70 to 1.07)	0.84 (0.69 to 1.03)
Poland: Wielkopolska	53.9	0.95 (0.54 to 1.66)	0.94 (0.58 to 1.53)
Portugal: Northern	47.1	0.83 (0.63 to 1.10)	0.81 (0.61 to 1.09)
Portugal: Lisbon	32.1	0.56 (0.42 to 0.75)	0.55 (0.42 to 0.73)
United Kingdom: Northern	62.6	1.10 (0.83 to 1.46)	1.16 (0.88 to 1.53)
United Kingdom: East Midlands	75.5	1.33 (1.19 to 1.47)	1.40 (1.27 to 1.54)
United Kingdom : Yorkshire & Humber	75.0	1.32 (1.17 to 1.48)	1.39(1.25 to 1.55)
Sweden: Stockholm	68.8	1.21 (1.02 to 1.43)	1.24 (0.99 to 1.55)

NOTES: 1. Adjusted for gestational age, sex, small for gestational age, multiple pregnancy, pregnancy complications, type of delivery, Apgar score, born on same day as maternal admission without in utero transfer
2. The sample average was used as the reference for deriving the RR for each region.

Table 3 In-hospital mortality and severe morbidity by receipt of all evidence-based practices

	In-hospital mortality (all neonatal admissions)	Severe morbidity (survivors to discharge)	Mortality or severe morbidity (all neonatal admissions)
All infants, N (%)	672/7336 (9.2)	669/6479 (10.3)	1341/7151 (18.8)
Not receiving evidence-based care, N (%)	431/3060 (14.1)	350/2552 (13.7)	780/2982 (26.2)
Receiving evidence-based care, N (%)	241/4276 (5.6)	319/3927 (8.1)	561/4169 (13.5)
Crude RR (95% CI)	0.42 (0.35 to 0.50)	0.56 (0.48 to 0.65)	0.51 (0.45 to 0.57)
Adjusted RR[1] (95% CI)	0.72 (0.60 to 0.87)	0.82 (0.71 to 0.94)	0.81 (0.72 to 0.90)
Propensity weighted RR[2] (95% CI)	0.72 (0.60 to 0.87)	0.87 (0.75 to 1.02)	0.82 (0.73 to 0.92)
Inborn infants[3], excluding deliveries on same day as admission, N (%)	464/5293 (8.8)	458/4695 (9.8)	911/5158 (17.9)
Not receiving evidence-based care, N (%)	282/1905 (14.8)	214/1579 (13.6)	495/1860 (26.6)
Receiving evidence-based care, N (%)	182/3388 (5.4)	244/3116 (7.8)	427/3298 (12.9)
Crude RR (95% CI)	0.39 (0.31 to 0.49)	0.54 (0.45 to 0.66)	0.49 (0.42 to 0.56)
Adjusted RR (95% CI)	0.72 (0.57 to 0.92)	0.83 (0.69 to 1.00)	0.81 (0.71 to 0.93)
Propensity weighted RR[2] (95% CI)	0.69 (0.55 to 0.87)	0.87 (0.72 to 1.06)	0.80 (0.70 to 0.92)

NOTES: 1. Adjusted for gestational age, sex, small for gestational age, multiple pregnancy, pregnancy complications, type of delivery, Apgar score, born on same day as maternal admission without in utero transfer and region 2.Adjusted on gestational age. 3. Infants hospitalised in a neonatal unit in the same hospital as the maternity unit (no neonatal transport in first 48 hours).

Table 4 - Predicted deaths and cases of severe morbidity if all infants or 90% of infants received all evidence-based practices

	Receiving evidence-based care n events (%)		Not receiving evidence-based care n events (%)		Total n events (%)		Reduction[1] n events (%)	
Observed								
Deaths	241	(5.6)	431	(14.1)	672	(9.2)		
Severe morbidity[2]	319	(8.1)	350	(13.7)	669	(10.3)		
Death and/or severe morbidity	561	(13.4)	780	(26.2)	1341	(18.8)		
If <u>all</u> infants received evidence-based care[3]								
Deaths	241	(5.6)	310	(10.1)	552	(7.5)	120	(17.9)
Severe morbidity[2]	319	(8.1)	285	(11.1)	604	(9.3)	65	(9.7)
Death and/or severe morbidity	561	(13.4)	629	(21.1)	1190	(16.6)	151	(11.3)
If <u>90%</u> infants received evidence-based care[3, 4]								
Deaths	241	(5.6)	352	(11.5)	593	(8.1)	79	(11.8)
Severe morbidity[2]	319	(8.1)	310	(12.1)	629	(9.7)	40	(6.0)
Death and/or severe morbidity	561	(13.4)	686	(23)	1247	(17.4)	94	(7.0)

NOTE: (1) Number and percent of events avoided (total observed – total predicted (2) Survivors only (3) Number of deaths and severe morbid events predicted from the final model adjusting for investigator selected covariables (4) The 10% of the sample who were assumed to not have evidence-based care were those with the lowest propensity scores – meaning least likely to receive evidence-based care because of their clinical or health care characteristics.