PROJECT FINAL REPORT

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Table of contents

List of tables

List of figures

1. Executive Summary

Context: Very preterm infants born before 32 weeks of gestational age (GA) face high risks of mortality and long-term neuro-developmental impairment. Rates of mortality and morbidity vary by a factor greater than two between European regions. The existence of these wide disparities suggests that substantial gains are possible using current medical knowledge.

Aims: to improve very preterm infants' survival and long-term health and development by ensuring that available medical knowledge is translated into effective perinatal care. Specific objectives are to build a knowledge base about how scientific evidence is translated into service provision in maternity and neonatal units by (1) measuring the use of key medical interventions, (2) identifying the factors associated with the use of these interventions and (3) investigating their effectiveness. The project also aims to assess decision-making processes and to propose strategies to achieve change.

Methods: Four studies were carried out on the use and impact of evidence-based interventions for very preterm infants in 19 regions in 11 countries with 850 000 annual births (Belgium, Denmark, Estonia, France, Germany, Italy, the Netherlands, Poland, Portugal, Sweden and the United Kingdom). 17 interventions were selected after review of the evidence using pre-established criteria.

Results: The project constituted a **European cohort of very preterm births** with a GA less than 32 weeks over a 12 month period in 2011/12 (6 months in France). Data on demographic and clinical characteristics, medical interventions and outcomes were collected until discharge from hospital (N=10,329 total inclusions, N=7,900 live births, and N=6792 discharged from hospital); Information on health and development at 2 years of corrected age were collected for 4421 babies using a parental questionnaire (response rate of 65.1%). This knowledge-base was completed by ***case studies*** of recommendations from regional governance bodies and professional societies about interventions for very preterm infants (N=160 documents)); ***unit studies*** of 134 neonatal units and 123 maternity units about policies and practices related to very preterm infants (99% and 92% of eligible units, respectively); and a ***qualitative study*** with in-depth interviews of doctors and nurses in neonatal units on processes for changing policies and practices.

Our study confirms the existence of wide regional disparities in health outcomes for very preterm infants which were unexplained by patient characteristics, even though these were highly diverse across regions. Very preterm infants continue to face high levels of in-hospital mortality (28.6% for all live and still births, 14.0 % for live births) and morbidity (10.5% of survivors had at least one severe neonatal morbidity). We found that there was an absence of standardized protocols and guidelines for many practices on national, regional and unit levels, even when these are backed by solid evidence. Our studies documented underuse of well proven evidence-based practices in all regions, including delivery in maternity units with specialised on-site neonatal care, administration of antenatal corticosteroids, hypothermia prevention and appropriate respiratory management at delivery. We showed that comprehensive use of these practices was associated with lower mortality and severe morbidity. Analyses also showed that having an evidence-based unit policy improved observed compliance. For other interventions (for instance, treatment of patent ductus arteriosus (PDA), caesarean delivery, $MgSO_4$ for neuroprotection), large regional treatment variations after adjustment for patient factors revealed the lack of consensus on best-practice and highlighted areas where guidance for clinicians is needed. Having high-quality evidence and showing an impact on infant health emerged as strong motivators for clinicians to change practices in the qualitative study.

Applications: The project provides actionable scientific knowledge on which to base strategies to improve the health of this high risk population. The project's findings have been disseminated to regional stakeholders and in international fora (>60 presentations). A stakeholders' dissemination workshop was held in October 2014 (≈65 attendees) to discuss the results and to identify salient themes for dissemination and intervention actions. The project enhances cooperation and excellence in Europe by creating a unique multiregional European cohort to provide continued knowledge for improving the health and wellbeing of children born very preterm.

2. Project context and objectives

2.1 Context: Evidence based care to improve health for very preterm infants in Europe

The EPICE "Effective Perinatal Intensive Care for very preterm infants in Europe" project's overriding aim is to improve the survival and quality of life of very preterm infants by ensuring that medical knowledge is translated into effective perinatal care, meaning care during pregnancy, delivery and the child's neonatal hospitalisation.

Very preterm birth is one of the principal determinants of infant death and childhood impairments in Europe.[1] Despite significant medical advances in recent decades, infants born before 32 weeks of gestation — about 1.5% of total births — remain at high risk of stillbirth, infant death and neurodevelopmental impairment, including cerebral palsy, cognitive delays and sensory loss (such as visual and auditory deficits). In Europe, rates of mortality and short-term morbidity vary by a factor greater than two between regions.[2 3] Studies find substantial variations in health outcome between neonatal intensive care units that are unexplained by clinical or socio-demographic factors.[4 5]

The existence of these wide disparities in very preterm risk-adjusted mortality and morbidity across countries and neonatal units suggests that substantial gains are possible using current medical knowledge.[2 4-7] 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 (EB) 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 organizational, cultural or personal barriers.[18-20] Moreover, while EB 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.

There is a longstanding tradition of clinical reviews in the fields of obstetrics and neonatology. The Cochrane Collaboration evolved from a British project for systematic reviews of perinatal trials in the mid-1970s to an international collaboration to develop the *Oxford Database of Perinatal Trials* in the 1980s, and among the first entities established within the Collaboration were the Cochrane Pregnancy and Childbirth and Cochrane Neonatal Groups.[21] Over 250 reviews are currently available from Cochrane Neonatal Reviews, more than half relevant to the care of very preterm infants.[22] They are regularly updated as new scientific information is produced. However, despite this tradition, there is relatively little research in Europe about how and to what extent this scientific knowledge is implemented in the care of very preterm infants or about the factors that are associated with the uptake of new recommendations.

Society's stakes in improving outcomes for these infants are high because of the long life expectancy associated with healthy survival, the permanent nature of impairments in case of disability, and the high economic and emotional costs for patients, their families and society. Between 5 and 10% of babies born before 32 weeks of gestation and discharged alive from hospital develop cerebral

palsy,[23-26] and even babies without severe disabilities face two-fold or greater risks of developmental, cognitive and behavioural difficulties in childhood. [27 28] Rates of impairment rise steeply with decreasing gestational age. In a European cohort of babies born before 26 weeks of gestation, rates of severe, moderate and mild disability were 22%, 24% and 34%.[29] In a US neonatal network, more than a third of babies born weighing less than 1000 grams had severe disabilities.[30] Very preterm birth also appears to be associated with adverse developmental programming that may increase the risks of hypertension,[31] diabetes[32] and chronic lung disease in later life.[33] Providing care for very preterm infants is expensive.[34] This financial burden on the health system was recently estimated in the UK at a surplus cost of £61 000 for a very preterm compared to a term survivor.[35] Implementing evidence-based guidelines and eliminating ineffective treatments improves the cost-effectiveness of these investments in health.

2.2 Objectives

1. **Build an empirical knowledge base** concerning how scientific knowledge about effective interventions and best clinical practices is translated into health service provision in maternity and neonatal units caring for very preterm infants in Europe. This will include:
    a. Measurement of the **rates and trends of use of key medical and nursing interventions** in clinical settings and comparison with state-of-the-art scientific knowledge about their effectiveness and side effects.
    b. Identification of the **factors associated with adoption of evidence-based practices**. These factors include characteristics of the patient, provider, institution, region and country as well as those specific to the intervention.
    c. Provision of **data on the effectiveness of different medical practices and policies** by comparing outcomes in terms of both overall survival and survival free from major morbidities at 2 years of age, corrected for prematurity

2. **Assess decision-making and knowledge implementation processes** within units and on the regional level to **identify catalysts for the uptake of evidence-based interventions** for selected medical interventions as well as reasons for continued use of unproven practices. Focus will also be placed on innovative approaches to the implementation of evidence-based practices.
3. **Propose methods and strategies to achieve behavioural changes** in the delivery of perinatal health care based on the analysis of current practices and the comparative assessment of models of dissemination and implementation of medical knowledge in health facilities in European countries. These proposals will form the basis for future evaluative research.

The project is implemented by a research consortium composed of:

- 11 partners representing 19 regions from 11 EU Member States and providing multi-disciplinary perspectives (obstetrics, paediatrics, epidemiology, health services research)
- External scientific advisors with expertise in key thematic areas.

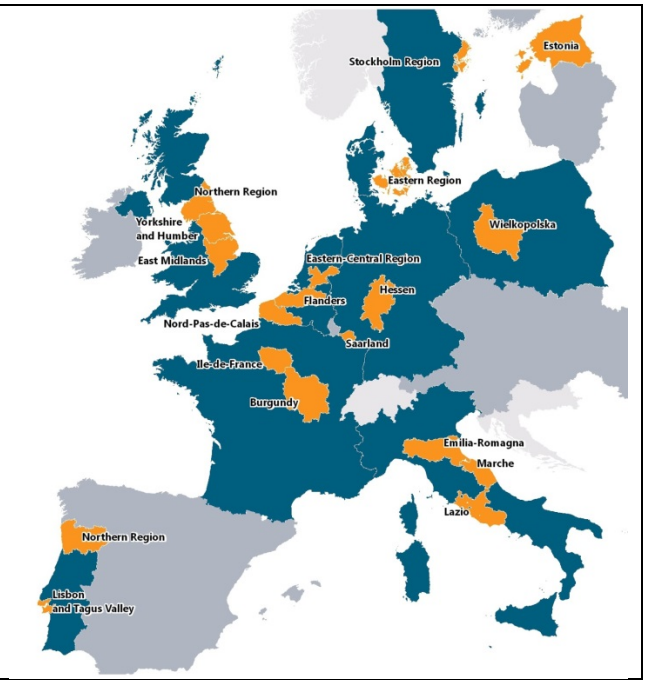
2.3 Methods and Approach

We used quantitative and qualitative approaches to build a knowledge base about the adoption of evidence-based medical interventions for the care of very preterm babies in 19 regions from 11 countries. Regions were selected with respect to three principal criteria: **geographic and organisational diversity**, **feasibility** (i.e. existing infrastructure and on-site expertise for implementing the study protocol), and **sample size considerations**. 10 of the 19 regions participated in the 2003 MOSAIC study of very preterm births. [6]

EPICE regions:

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 participating in the 2003 MOSAIC study of very preterm infants.



Four studies were conducted to collect data on the prevalence and determinants of evidence-based practices in the study regions at three levels: region, unit and patient.

(1) A **population-based prospective cohort study** of very preterm infants between 22 and 31 weeks of gestation to collect data on medical practices, clinical characteristics and health outcomes.

a. *Perinatal data collection.* Investigators abstracted data from medical records in obstetrical and neonatal units using a pretested standardized questionnaire with common definitions. Data were collected between April 2011 and September 2012; in each region inclusions occurred over 12 months, except in France (6 months). 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.

b. *Data collection at 2 years of corrected age*: This study used a parental questionnaire to collect assess data on health and development at 2 years of corrected age. The questionnaire was based on previously validated assessment tool, the PARCA R which in includes the MacArthur language assessment short form, and collects data on health, neuro-developmental outcomes, growth and socio-demographic information about the family.36 37 The questionnaire is organized in five sections: (1) Your child's play, (2) What your child can say, (3) Your child's health and development, (4) Your child's growth, (5) About your home and family. The instrument was pretested in all the regions in June and July 2012. We developed a long form and a short form language questionnaire, because the MacArthur short form verbal test was not available in some languages. In the French region, the Ages and Stages questionnaire (ASQ) for development was instead as this questionnaire has validated in France whereas the PARCA R has not. 38The questionnaire was translated into the different national local languages, and into languages of minority groups in several countries (Russian, Turkish and Romanian) where these represent a high the proportion of very preterm infants is high among minority groups.

(2) S**urvey of maternity and neonatal units** to collect the maternity and neonatal units that cared for very preterm infant. Data were collected by a structured postal questionnaire developed by the EPICE consortium and included information on the structural characteristics of units (level of specialization), their activity levels in 2011 policies, protocols and practices related to selected medical interventions, ethical decisions, decision making processes and existence of health-care quality monitoring systems. The questionnaire was sent to head of the units by post or e-mail. Several people within the unit could discuss responses and fill in the questionnaire. The questions were formulated in a way so that they could be answered in the same way by different members of staff. The questionnaire was pretested with neonatologists outside the study regions in all countries and then translated (and back translated) in Italy and France. It was administered in English in Belgium, Denmark, Estonia, Germany, the Netherlands, Poland, Portugal, Sweden and the United Kingdom. Neonatal units with at least 10 very preterm admissions per year and their associated maternity units were included in the unit study. These parameters were fixed before the study's onset based on available data about unit sizes.

(3) **Qualitative studies** in selected units to identify obstacles and facilitators for the uptake of evidence-based practices. The study focused on the decision-making process for the development, implementation and evaluation of clinical protocols and/or guidelines in neonatal intensive care units based on the most recent change that occurred to unit clinical guidelines or policies. It was carried out in: Denmark (Eastern region), France (Ile-de-France), Germany (Hesse), Italy (Lazio), Portugal (Northern), and UK (East Midlands). Only third level Neonatal Intensive Care Units (NICUs) were eligible. Units where members of EPICE Steering committee are based were excluded (which led to the exclusion of some regions from the study). In every region, two tertiary NICUs were randomly selected by the INSERM coordinating centre, with stratification for academic status, and invited to participate. We aimed at interviewing 4 staff members (2 physicians and 2 nurses) in each participating unit. 42 in-depth interviews were carried out.

(4) **Case studies of regional governance** as regards evidence-based practices. Case studies of the EPICE project aimed to describe and analyse national and regional laws and recommendations on the care of very preterm infants, in the 19 European regions participating to the study and at the European and international level, affecting use of evidence-based practices for the delivery of and care for very preterm infants. The case studies compiled information on regional, national, European and international governance structures (government structures and agencies, and scientific/professional societies), and included all regulations and recommendations issued by International, European, national, regional bodies which affect the care of women at risk of very preterm delivery and babies who are born very preterm. A standardised questionnaire developed by the EPICE consortium was completed by each region participating in the study. The coordinator of the project also completed a questionnaire for the governance structures at the European and international level.

2.4 Ethics

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). Separate authorisations were obtained for the 2 year follow-up and the qualitative studies.

3. Main Results

3.1 Interventions selected for the EPICE study

A broad list of 36 possible medical interventions of relevance to the care of very preterm infants was developed at the project's onset based on a review of the literature and contributions from the neonatologists and obstetricians in the EPICE consortium.

Criteria for selecting interventions were specified in the project proposal; Criteria 1 to 3 were considered particularly important. These were:

1. *Clinical importance:* the interventions have a significant impact on health outcomes and/or are widely implemented in many units.
2. *Quality of evidence*: well established evidence exists for their use (or non-use) from randomised controlled trials or observational data accompanied by expert reviews. Level of evidence was defined according to Oxford Centre for Evidence-based Medicine (CEBM). (http://www.cebm.net/index.aspx?o=1025). We also collected information on recommendations from European and national professional societies.
3. *Reliable and comparable indicators*: can be constructed in a standardised way in ALL units participating in the study to enable comparisons of practices (1) from information that can be recorded in medical records at the patient level (for the cohort study) and/or (2) from answers to structured questions in a questionnaire completed by the heads of departments (or their delegate) about the unit (for the maternity and neonatal unit study).
4. *Variability*: inter-regional and inter-unit variability in use of the intervention exists and suggests that non-clinical factors (treatment site, organisation of care, provider characteristics, for example) have an impact in decisions about implementation beyond medical knowledge about effectiveness.
5. *Availability of historical data*: a similar indicator of use was collected in the 2003 MOSAIC cohort.

To select the interventions, we first conducted an assessment exercise within the consortium to eliminate interventions which were not considered to be clinically important or for which there was no or only very sparse evidence (criteria 1 and 2). Participants in this process were obstetricians, neonatologists and epidemiologists from the study regions; A structured consensus process was used to achieve this goal and to develop a shortlist of interventions. At this point, consortium members were also asked to identify interventions that interested them most.

Based on the responses to this structured consensus process, experts from within the group were assigned to each intervention on the shortlist. These experts were responsible for creating a template document summarizing the evidence-base and for proposing indicators for measuring use of the intervention and that could be collected using data available in obstetrical or neonatal medical records in all study regions (Criteria number 3). Feasibility was a major determinant of the selection process at this stage. These reports were presented and discussed by the EPICE research consortium at a plenary meeting and used to select the indicators selected for the study. The document summarizing this process was submitted to the commission as a supporting document.

Table 1 presents the 17 EPICE study interventions with an assessment of the evidence-base and whether it was possible to develop indicators at the infant level and/or at the unit level. ***A first result which emerged from this process and that is reflected in this table is that there are a relatively limited number of interventions which are based on a high level of evidence.*** Some of the interventions retained for the study had an evolving evidence-base and were chosen because of their

clinical importance and our interest in assessing practices when contrasting evidence is available. The study also collected information from units on parental visiting regulations as well as post-discharge follow-up programs. However, these were not considered interventions because they cover a broad set of interventions and procedures and are more accurately defined as programmatic areas. However, they were included in the initial review and the knowledge base. We also decided at this stage not to include information on pain management in the NICU because of the existence of another European focused entirely on this subject [39] and because of the difficulty of measuring these interventions using medical records.

Table 1 Practices/interventions included in the EPICE study by level of evidence and data collection

	High level of evidence	data collected on use at infant level	Data collected on unit level
1. Delivery in maternity units with appropriate on-site neonatal intensive care services	X	X	
2. Antibiotics for preterm labor			X
3. Use of tocolysis			X
4. Administration of antenatal corticosteroids	X	X	X
5. Magnesium sulphate as a neuroprotective		X	X
6. Delivery by cesarean section for VPT		X	X
7. Time (early or late) for cord clamping	X	X	X
8. Hypothermia prevention	X	X	
9. Surfactant Replacement Therapy	X	X	X
10. Inhaled Nitric Oxide (NO)			X
11. Breastfeeding and breast milk use	X	X	X
12. Probiotic Use			X
13. Management of patent ductus arteriosus (PDA)		X	
14. Kangaroo care (skin-to-skin)		X	
15. BPD prevention strategies (vitamin A/Caffeine)			X
16. Postnatal corticosteroids (non use)	X	X	X
17. ROP screening and treatment	X	X	X

NOTE: * associated with necrotizing enterocolitis, data only available on use of BF for first enteral feed and at discharge. Not sufficient for measuring overall use during hospitalization.

In conclusion, the EPICE consortium achieved consensus on a set of 17 interventions related to both obstetric and neonatal care of very preterm infants as well as 2 programme areas for inclusion in case, unit and cohort studies.

3.2 The regulatory environment: results from the case studies

The case studies compiled information on regional, national, European and international governance structures (government structures and agencies, and scientific/professional societies), and included regulations and recommendations issued by International, European, national, regional bodies which affect the care of women at risk of very preterm delivery and babies who are born very preterm with a focus on the interventions selected for inclusion in the EPICE study. We considered documents in force during the study period of the EPICE cohort (2011/2012) in the 19 European regions.

Table 2 describes the governance structures identified in each of the countries/regions classified into those which were government structures, agencies or public health authorities and professional

societies. This list illustrates the variability in the types of institutions that were considered as potential sources of guidelines/recommendations in the countries.

Table 2 Governance structures that issue guidelines on the health of pregnant women and newborns

Country	Region (s)	Goverment/Ministry/other	Agencies/Public Authorities	Professional societies
Belgium	Flanders	Belgian Health Care Knowledge Centre (KCE) Royal Decrees INAMI (Health Insurance) High Commission on Health Belgian Advisory Committee on Bioethics	"Child and Family" agency	Doctors college for the mother and the newborn Flemish Society of Obstetrics and Gynecology Flemisch Society of Pediatrics Belgian Society of Neonatology
Denmark	Eastern Denmark		National Health Board	
Estonia		Ministry of Social Affaires Estonian Health Insurance Sick Fund		Estonian Gynaecologists Society Estonian Perinatal Society
France	Nord Burgundy Ile-de-France	Ministère de l'emploi et de la solidarité Ministère de la santé, de la jeunesse et des sports	Haute Autorité de santé (HAS) AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) AFSSA (Agence Française de Sécurité Sanitaire des Aliments)	Société Française de Néonatologie Collège national des gynécologues et obstétriciens français Société Française de Pédiatrie
Germany	Hesse Saarland		GBA	Association of German Scientific Medical Societies.
Italy	Lazio	Ministero della Salute Istituto Superiore di Sanità (ISS)	Assessorato alla Sanità Regione Lazio LazioSanità- Agenzia di Sanità Pubblica	Società Italiana di Neonatologia Società Italiana Medicina Perinatale (SIMP)
Italy	Emilia Romagna			
Italy	Marche			
The Netherlands	Central and East	Health Care Inspectorate	National Health Council	Dutch Paediatric Association Dutch Society for Obstetrics and Gynaecology Perinatal Registry Netherlands
Poland	Wielkopolska	Ministry of Health Wilkopolska regional government	Mother and child institute Central Office of Statistics	
Portugal	Northern Region Lisbon Targs Valley	National Law Ministry of Health		Portuguese Society of Neonatology
United Kingdom	Northern Region East Midlands Yorkshire and Humble		NICE NHS	
Sweden	Stockholm	The Swedish Association of Local Authorities and Regions Stockholm county council	The National Board of Health and Welfare Swedish Council on Health Technology Assessment The Swedish National Council on Medical Ethics	Swedish Society of Medicine Swedish Soc for Obstetrics and Gynecology Swedish Neonatal Society Swedish society of pediatric cardiology

Table 3 shows the documents that were identified as part of the case studies in each region. A total of 105 laws and recommendations on the EPICE interventions were found. The majority of documents were published by obstetric or paediatric professional societies, or by governmental structures, mainly Ministries of Health, and Health Agencies. One of the interventions (hypothermia) was not included in this survey because it was added to our list of interventions after the survey had been developed.

Table 3 Number of documents by EPICE intervention

EPICE Interventions	N
Delivery in tertiary centres	9
Antibiotics for preterm labour	14
Tocolysis	13
Administration of antenatal corticosteroids	14
Magnesium sulphate as a neuroprotective	2
Delivery by caesarean section for VPT	7
Time (early or late) for cord clamping	2
Surfactant Replacement Therapy	13
Inhaled nitric oxide	2
Breastfeeding and breast milk use for VPT	15
Probiotic Use	0
Management of patent ductus arteriosus (PDA)	5
Kangaroo care (skin-to-skin)	2
BPD prevention strategies (vitamin A/Caffeine)	1
Postnatal corticosteroids (non use)	4
Rethinopathie of prematury (ROP) screening and	10
TOTAL	115*

*Some documents may be counted more than once if they refer to different interventions
Data on hypothermia prevention not included

Figure 1 shows the number of countries with at least one law or recommendation by intervention. National recommendations for the use of antenatal steroids existed in all the EPICE regions. A majority of the countries had at least one recommendation for obstetric interventions (delivery in tertiary centres, use of tocolytics, antibiotics for preterm labour, delivery by C-section for very preterm infants). Documents were also common in most of the countries for ROP screening and treatment, use of surfactant replacement therapy and for breastfeeding of very preterm infants. No country had documents for the use of probiotics.

Figure 2 shows the number of interventions covered by at least one law or recommendation by country, ranged by the number of interventions covered. Our data shows that some of the regions included in our project have a more extensive regulatory context, which include more than half of the interventions included in EPICE covered (Italy, the UK, Germany, Portugal, France and Sweden), than regions where few interventions were covered (Poland, Denmark, Belgium, Estonia and the Netherlands)

This analysis also underscored the prominent role of scientific and professional societies in establishing regional and national governance related to very preterm infants, as shown in Figure 3.

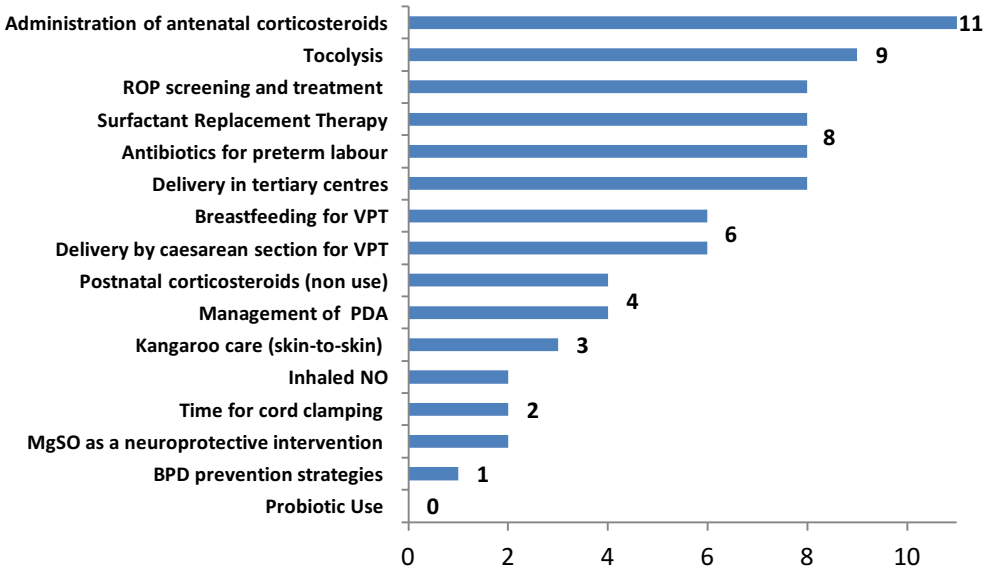


Figure 1 Number of countries with at least one document by intervention

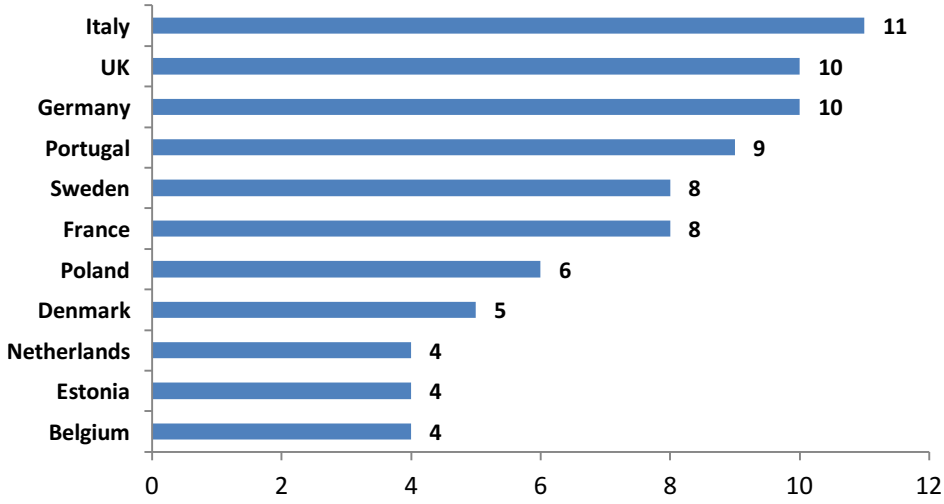


Figure 2 Number of EPICE interventions by country

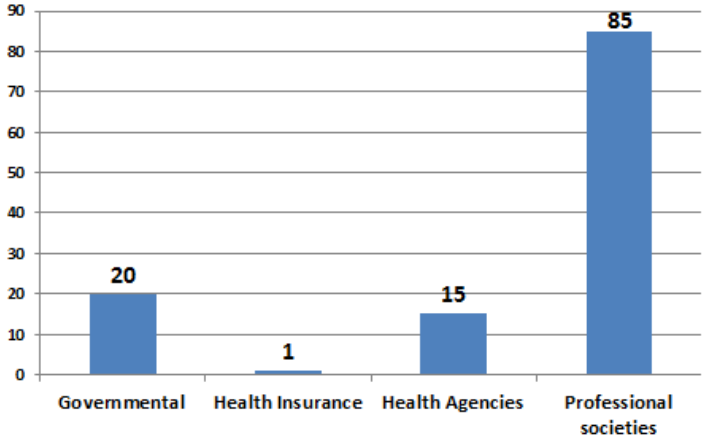


Figure 3 Number of recommendations by governance structure

In conclusion, there were more guidelines on obstetric interventions than on neonatal interventions. For some interventions – antenatal corticosteroid administration, use of tocolytics – guidelines exist everywhere or almost everywhere, whereas for others, there are almost no guidelines (probiotic use, timing of cord clamping). The interventions that are not represented are those with a less solid evidence base. However, some interventions for which the evidence-base was considered to be strong had few governance guidelines (non-use of postnatal corticosteroids). Professional and scientific societies were the principal contributors to the regulatory environment. Regional governance of evidence-based care for very preterm infants was varied across regions.

3.3 Inclusions in the cohort and unit studies

The EPICE cohort included 10329 total births of which 7900 were live births, and 1614 were stillbirths and 815 were terminations of pregnancy. Total inclusions varied from 134 in Marche (Italy), 143 in Burgundy (France) and 150 in Saarland (Germany) to 1468 in Ile-de-France (France), 990 in Flanders (Belgium) and 921 in the Yorkshire and Humber region.

Terminations of pregnancy were included in most of the EPICE regions. However, they could not be collected in the German and Italian regions, although Lazio region provided information from a separate register. The rates of terminations of pregnancy differ greatly in the EPICE cohort, reflecting different policies related to congenital anomaly screening during pregnancy (and in particular the timing of the 2nd trimester ultrasound, which is scheduled later in some countries, notably France). They also reflect differences in the regulations and practices related to late termination. Terminations of pregnancy are not legal in Poland at any gestational age, except in rare circumstances, as is also the case in Sweden and Estonia after 21 weeks of gestation

Table 4 Number of inclusions into the EPICE study by outcome of pregnancy in 19 European regions

Region	Total VPT births N	TOP N	Still births N	Live births N	Labor ward deaths N	Deaths in neonatal unit N	Total neonatal deaths N	Total dischaged alive N
BE:Flanders	990	70	168	752	34	65	99	653
DE:Hesse	705	NA	88	617	9	65	74	543
DE:Saarland	150	2	7	141	3	19	22	119
DK:Eastern	441	25	65	351	15	50	65	286
Estonia	179	0	26	153	0	12	12	141
FR:Burgundy	143	26	23	94	4	10	14	80
FR:IDF	1468	285	282	901	68	79	147	754
FR:Northern	436	56	68	312	16	21	37	275
IT: Emilia	511	NA	53	458	6	53	59	399
IT:Lazio	754	73	109	572	13	81	94	478
IT:Marche	134	NA	30	104	1	5	6	98
NL:East-Central	550	87	70	393	21	41	62	330
PL:Wielkopolska	400	7	77	316	10	56	66	250
PT:Lisbon	578	50	89	439	6	73	79	360
PT:Northern	396	45	66	285	5	33	38	247
SE:Stockholm	308	0	41	267	10	16	26	241
UK: East Mid	739	38	123	578	21	47	68	510
UK: Northern	526	18	85	423	1	39	40	382
UK:Yorkshire	921	33	144	744	20	78	98	646
Total	10329	815	1614	7900	263	843	1106	6792

NOTE – (1) missing outcome: 2 missing in Lisbon, 1 missing in Porto, 1 missing UK Northern (2) TOP were not collected in Germany and Italy

More than 740 000 births occurred in the EPICE regions during the study period (Table 2). In France, data only cover the 6 month inclusion period. The overall very preterm birth rate was 12.8 live and stillbirths per 1000 total births and 10.7 live very preterm births per 1000 live births. This total very preterm birth rate ranged from 8 to 18, although most regions had values in the range of 11.0-15.0 per 100 total births (14/19). The rate of stillbirths per 1000 total births was 2.2, with regional variations from 0.9 to 3.1. These data are consistent with national statistics from European countries. Overall stillbirth rates in European countries are on average 4.0 per 1000 total births and these very early deliveries contribute to about half of this rate. [40]

Table 6 presents data on the inclusions in the follow-up study. Of the 6792 babies discharged home alive, 4421 were included in the follow-up study. Some of the babies were not eligible for follow-up – primarily because they refused follow-up (n=314) or because consent could not be obtained (n=22). A further 34 babies died after discharge. The follow-up rate was 65.1% with wide variations between regions. Eight regions had follow-up rates of 80% or more, 7 between 50% and 70% and 4 less than 50%. These differences reflect health service factors (where follow-up was already organized, it was easier) and organisational factors (some regions were able to centralize follow use telephone calls to reach non-responders), but also seem to reflect cultural differences: cohort studies in the UK, such as the EPICure Study have not been able to attain high follow-up despite considerable efforts.[41]

Table 5. Very preterm total birth rate and live birth rate in the EPICE regions

Region	Total births N	Total live births N	VPT live births N	VPT still and live births N	VPT still and live birth rate per 1000 total births	VPT stillbirth rate per 1000 total births	VPT live birth rate per 1000 live births
BE:Flanders	69605	69277	752	920	13.2	2.4	10.9
DE:Hesse	48999	48823	617	705	14.4	1.8	12.6
DE:Saarland	7583	7567	141	148	19.5	0.9	18.6
DK:Eastern	31195	31052	351	416	13.3	2.1	11.3
Estonia	14940	14880	153	179	12.0	1.7	10.3
FR:Burgundy*	8776	8708	94	117	13.3	2.6	10.8
FR:IDF*	92105	91142	901	1183	12.8	3.1	9.9
FR:Northern*	28460	28199	312	380	13.4	2.4	11.1
IT: Emilia	40487	39751	458	511	12.6	1.3	11.5
IT:Lazio	54676	54491	572	681	12.5	2.0	10.5
IT:Marche	14281	13542	104	134	9.4	2.1	7.7
NL:East-Central	53854	53585	393	463	8.6	1.3	7.3
PL:Wielkopolska	38246	38082	316	393	10.3	2.0	8.3
PT:Lisbon	31238	31127	439	528	16.9	2.8	14.1
PT:Northern	31609	31525	285	351	11.1	2.1	9.0
SE:Stockholm	28624	28520	267	308	10.8	1.4	9.4
UK: East Mid	53100	52835	578	701	13.2	2.3	10.9
UK: Northern	34170	33975	423	508	14.9	2.5	12.5
UK:Yorkshire	61693	61385	744	888	14.4	2.3	12.1
Total	743640	738464	7900	9514	12.8	2.2	10.7

NOTE * study took place over 6 months

Table 7 presents the inclusions into the unit studies. A total of 532 maternity units and 270 neonatal units were located in participating regions, of which 135 and 135 respectively fulfilled study criteria, which was at least 10 VPT neonatal admissions in the neonatal unit. Response rates were good (134/135 for neonatal units and 124/135 for maternity units).

Table 6 Inclusions in the follow-up study

Region	Number of children included	Discharged alive		Refusing to participate	Consent for follow-up not obtained	Death after discharge		Non responder		Responder	
	N	n	%	n	n	n	%	n	%	n	%
BE:Flanders	990	653	66,0	13	NA	0	0,0	347	53,1	306	46,9
DK:Eastern	441	286	64,9	NA	NA	0	0,0	106	37,1	180	62,9
Estonia	179	141	78,8	0	0	2	1,4	1	0,7	138	97,9
FR:Northern	436	275	63,1	5	NA	1	0,4	39	14,2	235	85,5
FR:Burgundy	143	80	55,9	3	NA	0	0,0	8	10,0	72	90,0
FR:IDF	1468	754	51,4	30	NA	5	0,7	70	9,3	679	90,1
DE:Hesse	705	543	77,0	111	NA	6	1,1	170	31,3	367	67,6
DE:Saarland	150	119	79,3	37	NA	0	0,0	52	43,7	67	56,3
IT:Lazio	754	478	63,4	18	8	3	0,6	180	37,7	295	61,7
IT:Emilia	511	399	78,1	1	NA	3	0,8	41	10,3	355	89,0
IT:Marche	134	98	73,1	1	NA	1	1,0	16	16,3	81	82,7
NL:East-Central	550	330	60,0	4	2	2	0,6	99	30,0	229	69,4
PL:Wielkopolska	400	250	62,5	NA	0	1	0,4	50	20,0	199	79,6
PT:Northern	396	247	62,4	6	1	1	0,4	48	19,4	198	80,2
PT:Lisbon	578	360	62,3	40	20	1	0,3	150	41,7	209	58,1
UK:Northern	526	382	72,6	NA	NA	2	0,5	277	72,5	103	27,0
UK:East Midlands	742	510	68,7	45	19	1	0,2	256	50,2	253	49,6
UK:Yorkshire and Humber	918	646	70,4			4	0,6	352	54,5	290	44,9
SE:Stockholm	308	241	78,2	0	0	1	0,4	75	31,1	165	68,5
Total	10329	6792	65,8	314	22	34	0,5	2337	34,4	4421	65,1

Table 7 Maternity and Neonatal units in the EPICE study regions

	Maternity units			Neonatal units		
Region	Total	Eligible*	Responded	Total	Eligible*	Responded
BE:Flanders	67	9	9	45	9	9
DE:Hesse	56	12	11	15	12	12
DE:Saarland	10	2	2	6	2	2
DK:Eastern	8	8	8	10	8	8
Estonia	21	4	2	7	4	4
FR:Burgundy	14	1	1	6	1	1
FR:IDF	98	15	15	30	16	16
FR:Northern	35	6	6	12	6	6
IT: Emilia	31	9	9	11	9	9
IT:Lazio	47	12	10	13	12	12
IT:Marche	18	2	2	4	1	1
NL:East-Central	12	2	2	18	2	2
PL:Wielkopolska	36	4	4	13	4	4
PT:Lisbon	17	8	8	13	8	8
PT:Northern	13	9	9	10	9	9
SE:Stockholm	6	5	5	6	4	4
UK: East Mid	15	11	8	22	11	11
UK: Northern	11	5	4	12	5	5
UK:Yorkshire	17	11	8	17	12	11
TOTAL	532	135	123	270	135	134

3.4 Description of characteristics and health outcomes of infants in the EPICE cohort

Characteristics of very preterm births in European regions

The characteristics of the population of very preterm infants were highly diverse across regions, as shown in Figures 4 and 5 which present maternal and pregnancy factors. These figures provide the average of the cohort for each indicator as well as the values observed in the 2 regions with the lowest and highest values.

Among the women giving birth to very preterm infants, 26% were aged 35 or over, but this ranged from close to 50% to fewer than 15%. Primiparous women were 55% of the sample with a range from 45% to 66%. The variation in the contribution of the immigrant population was particularly striking, from 1% to 48% with an average of 23%. The difference in maternal characteristics was echoed in those of the neonates with a differing prevalence of pregnancy complications, multiple births and extremely preterm births less than 26 weeks of GA.

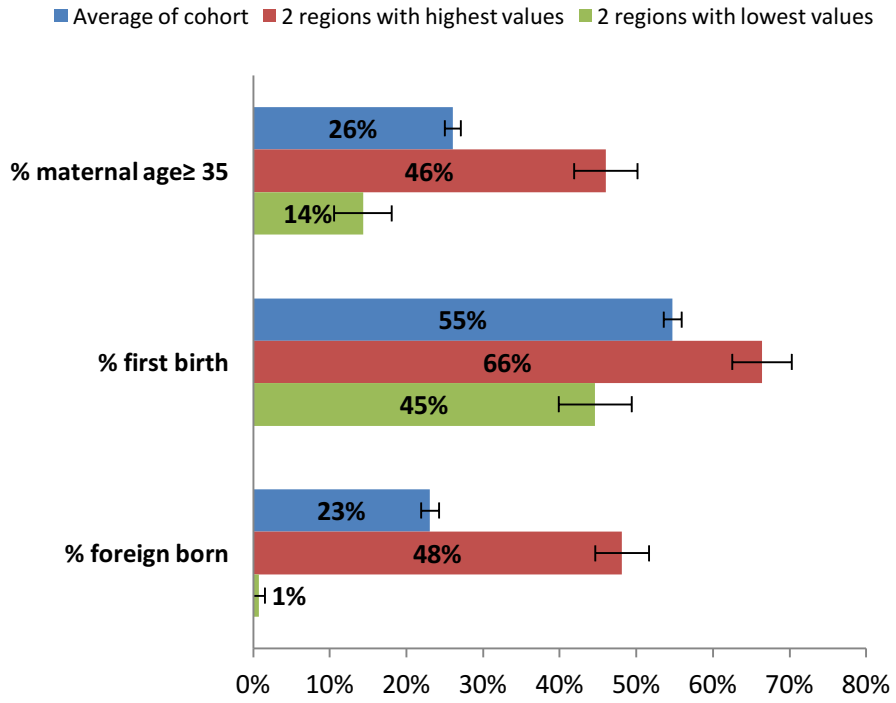


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Figure 4: Maternal characteristics, live very preterm births

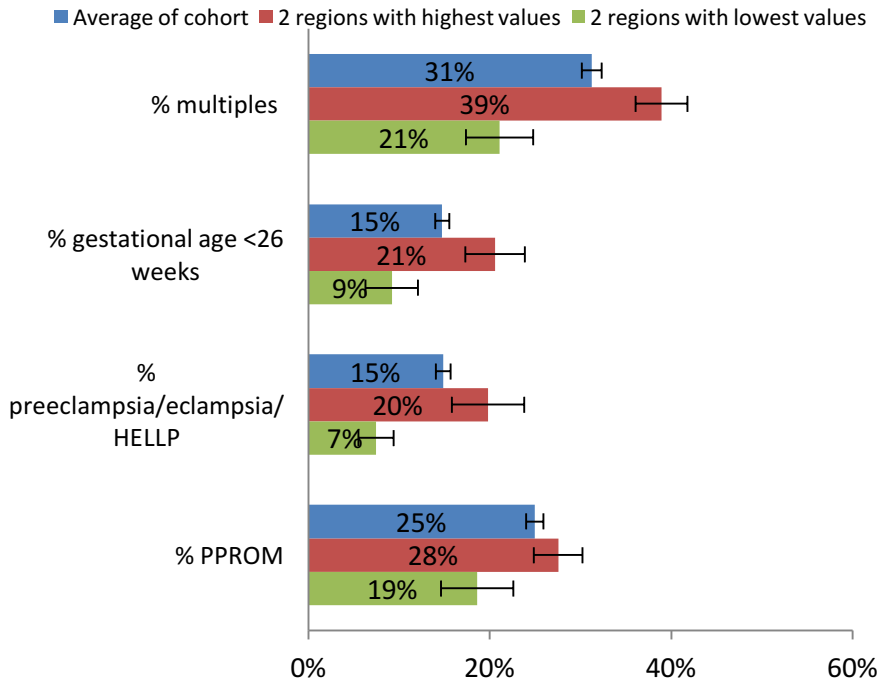

Figure 5: Pregnancy characteristics, live very preterm infants

Survival and major neonatal morbidity

Survival to discharge was 71.4% of all births and 86.0% of live births (Table 8). This proportion after live birth varied from 79% in the Polish region to more than 90% in Stockholm, Estonia and Marche. For survival with respect to all births, the range was: 64% to 81%.

Table 8. Survival to discharge in 19 European regions

Region	Still births N	Live births N	Total dischaged alive N	Survival % of still and live births	Survival % of live births
BE:Flanders	168	752	653	71.0	86.8
DE:Hesse	88	617	543	77.0	88.0
DE:Saarland	7	141	119	80.4	84.4
DK:Eastern	65	351	286	68.8	81.5
Estonia	26	153	141	78.8	92.2
FR:Burgundy	23	94	80	68.4	85.1
FR:IDF	282	901	754	63.7	83.7
FR:Northern	68	312	275	72.4	88.1
IT: Emilia	53	458	399	78.1	87.1
IT:Lazio	109	572	478	70.2	83.6
IT:Marche	30	104	98	73.1	94.2
NL:East-Central	70	393	330	71.3	84.0
PL:Wielkopolska	77	316	250	63.6	79.1
PT:Lisbon	89	439	360	68.2	82.0
PT:Northern	66	285	247	70.4	86.7
SE:Stockholm	41	267	241	78.2	90.3
UK: East Mid	123	578	510	72.8	88.2
UK: Northern	85	423	382	75.2	90.3
UK:Yorkshire	144	744	646	72.7	86.8
Total	1614	7900	6792	71.4	86.0

NOTE – (1) missing outcome: 2 missing in Lisbon, 1 missing in Porto, 1 missing UK Northern (2) TOP were not collected in Germany and Italy

The distribution of severe neonatal morbidity is presented in Table 9 for infants discharged alive by region. Severe neonatal morbidity comprised intraventricular haemorrhage (IVH) grade III or IV, cystic periventricular leukomalacia (cPVL), retinopathy of prematurity (ROP) stages III to V, and severe necrotizing enterocolitis (NEC). IVH grades were determined using Papile's classification[42] and periventricular leukomalacia was recorded only if cystic abnormalities were present on ultrasound or MRI scan. Severe NEC was assessed by surgery or peritoneal drainage because Bell stages were not routinely recorded in all regions. We did not include all bronchopulmonary dysplasia (BPD) because large regional variability in respiratory management and oxygen saturation targets affect rates of this outcome variable.[43] We defined an indicator of severe BPD was defined as BPD with a FiO2>29% but this was not available in two UK regions where this information was not recorded in medical records. Any morbidity without severe BPD was 10.5% in the sample, with regional ranges from 7.3% to 23.5% while severe morbidity with severe BPD was present in 11.7 of survivors to discharge in the 17 regions with these data (regional range from 9.3% to 23.5%)

We also measured developmental delay at 2 years of age among the children in the follow-up. As the protocols differed slightly between the regions, we used the following measures for the follow-up: gross motor impairment, severe visual impairment, severe to moderate hearing impairment, a low non-verbal PARCA R score, defined as a value less than 22, and a "no" response to the question, does your child say more than 10 words. The full PARCA R (which includes a non-verbal and verbal score) could not be completed in countries without a translation of the MacArthur short form (Belgium, Eastern Denmark, the Netherlands, Wiekopolska, Portugal and Stockholm) and therefore the question on language which was asked in all regions was used. In the German, Italian and UK regions

as well as Estonia, the complete PARCA score could be derived. In France, the PARCA-R was not used, so they are excluded from the overall composite.

Measures of neurodevelopmental impairment are based on the British Associaiton of Perinatal Medicine (BAPM) 2008 system: one or more of vision, hearing, gross motor or cognitive impairment where Gross motor impairment is defined as unable to walk without assistance or aides or unable to sit without support or unable to hold head up without support and Vision impairment is blind or sees light only and Hearing impairment Child does not hear normally, needs a hearing aid.

Table 10 provides data on developmental delay for the regions. Missing cases ranged from 1 to 4 % and are excluded from calculation of percentages. The table shows that not all children were assessed at exactly 24 months of corrected age and some differences existed between regions. We also present the percent of a children with any delay in the last column for the entire sample and those within a +/- two month window. There are not major differences in the estimates. The proportion of children with any delay ranged from about 20% to around 35%.

There are wide differences in the very preterm population's characteristics across European regions as well as their mortality and short term morbidity and longer term development. These results raise questions about whether maternal and neonatal demographic and clinical characteristics are responsible for the observed differences in outcome.
These results also illustrate the importance of taking these differences into account when evaluating interventions, especially those likely to be influenced by social and clinical characteristics, such as breastfeeding, for instance, and to consider the possibility that there may be an interaction between population characteristics and health care or health and development.

Our study also confirms previous research illustrating large variability in outcomes. This finding refers to all outcomes in this study: stillbirth, in-hospital mortality after live birth, severe neonatal morbidity and developmental delay at 2 years.

Table 9 Severe neonatal morbidity among very preterm infants born at less than 32 weeks of gestation surviving to discharge in 16 European regions

	IVH-III/IV	cPVL	ROP	Severe NEC	Severe BPD	Any wo BPD	Any w BPD
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
All regions	250/6364 (3.9)	203/6370 (3.2)	236/6346 (3.7)	119/6422 (1.9)	136/5013 (2.7)	663/6303 (10.5)	575/4934 (11.7)
Belgium: Flanders	17/638 (2.7)	21/648 (3.2)	24/637 (3.8)	8/651 (1.2)	16/640 (2.5)	61/624 (9.8)	70/614 (11.4)
Denmark: Eastern	9/278 (3.2)	4/278 (1.4)	9/277 (3.2)	6/286 (2.1)	11/263 (4.2)	24/271 (8.9)	29/252 (11.5)
Estonia	4/140 (2.9)	8/140 (5.7)	12/140 (8.6)	4/140 (2.9)	4/140 (2.9)	21/140 (15)	23/140 (16.4)
France: Northern	6/275 (2.2)	9/275 (3.3)	5/274 (1.8)	2/275 (0.7)	12/243 (4.9)	21/274 (7.7)	30/243 (12.3)
France: Ile-de-France	31/745 (4.2)	16/746 (2.1)	2/741 (0.3)	1/746 (0.1)	10/692 (1.4)	46/740 (6.2)	53/689 (7.7)
Germany: Hesse	12/527 (2.3)	11/525 (2.1)	23/525 (4.4)	15/528 (2.8)	7/516 (1.4)	51/526 (9.7)	48/515 (9.3)
Italy: Lazio	17/470 (3.6)	16/470 (3.4)	24/465 (5.2)	6/472 (1.3)	10/458 (2.2)	54/467 (11.6)	55/455 (12.1)
Italy: Emilia	15/389 (3.9)	9/389 (2.3)	18/391 (4.6)	6/391 (1.5)	9/386 (2.3)	39/389 (10)	40/384 (10.4)
Netherlands: East-Central	15/328 (4.6)	9/327 (2.8)	4/326 (1.2)	6/329 (1.8)	10/327 (3.1)	30/326 (9.2)	36/326 (11)
Poland: Wielkopolska	21/236 (8.9)	22/235 (9.4)	24/234 (10.3)	11/236 (4.7)	1/236 (0.4)	55/234 (23.5)	55/234 (23.5)
Portugal: Northern	12/246 (4.9)	12/246 (4.9)	14/246 (5.7)	4/246 (1.6)	7/245 (2.9)	28/246 (11.4)	32/245 (13.1)
Portugal: Lisbon	16/360 (4.4)	12/360 (3.3)	14/359 (3.9)	7/360 (1.9)	11/359 (3.1)	41/359 (11.4)	44/358 (12.3)
UK: Northern	12/351 (3.4)	5/357 (1.4)	16/354 (4.5)	14/380 (3.7)	19/276 (6.9)	37/337 (11)	35/252 (13.9)
UK: East Midlands	28/507 (5.5)	18/505 (3.6)	14/507 (2.8)	12/507 (2.4)	--	58/505 (11.5)	--
UK: Yorkshire & Humber	27/638 (4.2)	25/633 (3.9)	25/637 (3.9)	14/638 (2.2)	--	80/633 (12.6)	--
Sweden: Stockholm	8/236 (3.4)	6/236 (2.5)	8/233 (3.4)	3/237 (1.3)	9/232 (3.9)	17/232 (7.3)	25/227 (11)

Table 10 Neurodevelopmental outcomes at follow-up with information on average corrected age and percent22 to 26 months

Region		Corrected age		22-26 months	Gross motor impairment	Visual impairment	Hearing impairment	PARCA <22	<10 words	Any delay	Any delay, assessed 22-26 mos
	N	m	sd	%	%	%	%	%	%	%	%
BE:Flanders	308	23.5	1.1	97.3	6.9	0.7	1.0	18.5	8.7	24.7	24.8
DK:Eastern	180	23.4	1.8	87.0	2.8	0.6	0.6	15.0	9.5	27.0	26.1
Estonia	138	23.7	0.8	99.3	9.6	0.0	0.0	10.9	8.7	20.7	20.9
FR:Northern	235				10.7	0.4	1.8				
FR:Burgundy	72				13.6	0.0	1.4				
FR:IDF	679				8.8	0.5	0.3				
DE:Hesse	368	24.4	2.4	85.3	7.7	0.3	1.1	11.0	7.7	18.6	18.9
DE:Saarland	67	24.0	2.3	89.5	16.7	3.0	3.1	19.4	16.9	26.1	27.1
IT:Lazio	295	25.0	3.1	76.9	7.5	0.0	1.1	14.6	10.8	24.1	27.4
IT:Emilia	355	23.7	1.9	88.2	6.5	1.7	0.8	15.2	11.5	22.5	23.3
IT:Marche	81	23.9	2.1	87.6	3.7	0.0	0.0	12.3	11.1	23.5	23.9
NL:East-Central	229	23.7	1.9	92.1	4.4	0.0	0.0	9.2	8.9	16.9	16.8
PL:Wielkopolska	199	23.7	0.5	100.0	10.7	0.5	2.0	24.4	18.6	36.6	36.6
PT:Northern	198	24.3	1.0	95.4	3.1	0.0	0.0	14.3	6.7	19.6	20.3
PT:Lisbon	209	24.4	1.4	91.9	4.0	0.0	0.5	15.5	10.4	24.2	25.1
UK:Northern	103	23.9	1.7	97.1	14.0	1.0	2.0	14.6	9.4	31.9	32.3
UK:East Mid	253	24.8	3.1	87.3	7.6	0.8	2.1	16.3	11.5	28.1	28.5
UK:Yorkshire and Humb	290	25.3	4.0	79.0	12.6	0.3	0.0	18.0	14.5	34.1	31.6
SE:Stockholm	165	23.8	0.6	100.0	4.9	0.0	0.0	20.2	11.3	28.9	28.9
Total	4424	24.2	2.3	89.7	7.8	0.5	0.8	15.5	10.7	24.9	25.3

3.5 Analyses: Explaining differences in mortality and morbidity between the EPICE regions

Several analyses were undertaken to determine the causes and the consequences of the wide variations in mortality observed in the cohort. We first sought to assess the extent to which maternal and neonatal demographic and clinical characteristics affected mortality rates. We also explored the initiation of active management of preterm births close to the limits of viability and how this influenced mortality and morbidity. A final analysis investigated the hypothesis that higher mortality is associated with lower morbidity among survivors.

The contribution of maternal and neonatal characteristics to mortality differences

In this analysis, outcomes for the EPICE cohort were defined in terms of the type and timing of death or survival to discharge from neonatal care using the following categories: stillbirth, deaths within the first 12 hours, deaths from 12 hours up to and including 7 completed days, deaths after 7 days and survivors from neonatal care. TOPs for congenital anomaly and other births associated with severe congenital anomalies were excluded. Data were excluded for the three regions where there were less than 150 cases: Saarland (Germany), Marche (Italy) and Burgundy (France). Maternal characteristics were maternal age, parity, multiple pregnancy and pregnancy complications defined as hypertensive pathologies (pre-eclampsia, eclampsia and HELLP syndrome), antepartum haemorrhage and preterm rupture of the membranes, iatrogenic delivery i.e. following induction of labour and/or caesarean section. Baby characteristics were gestational age at birth, birth weight, sex, twin or triplet and fetal growth restriction defined as fetal weight less than the 10th centile.

Crude in-hospital mortality rates for the total very preterm birth cohort of live and stillbirths 22+0 to 31+6, ranged from 19.5% to 48.9% by region whereas for all live births this was 6.7-20.9% and for admissions to neonatal care: 4.9-18.3%. Following adjustment for maternal and infant characteristics the variation in these rates reduced to: total cohort 23.5-39.3%; live births 10.2-17.7% and NIC admissions 7.5-15.2%. This study concluded that, despite the diversity in maternal and neonatal characteristics in the EPICE regions, only a small proportion of the variation in mortality rates was explained by maternal and infant characteristics. When the analysis was carried out by timing of death, the most marked differences between crude and adjusted rates were for stillbirths.

The mortality analysis was led by Elizabeth Draper and Brad Manktelow.

Active management at the limits of viability

Decisions governing active management of babies born at extremely low gestational ages are known to contribution to international variations in outcomes.[44 45] Two analyses were undertaken to explore the contribution of these factors to mortality and morbidity in the EPICE cohort.

The first focused on births between 22 and 25 weeks of gestation. Analyses were restricted to 12 regions in 5 of the countries because of sample size considerations at these low gestational ages (Belgium, France, Italy, Portugal and the United Kingdom). Out of the 1449 reported live births and fetal deaths between 22+0 and 25+6 weeks gestation born in 2011-2012, we investigated the percentage of births that were live born and those that received antenatal steroids and respiratory support as well as survival to discharge (with or without major neurologic and respiratory morbidities). We found that management varied widely between countries by gestation and birth weight. At 22 weeks gestation and 23 weeks when birthweight was less than 500 g, outcomes were consistently poor and there was little active management, as measured by use of respiratory support. However, there were marked differences between the regions in the active management of infants born at 23 weeks with a birthweight of 500 g or more. Similarly, practice varied

internationally for babies weighing less than 500g born at 24 and 25 weeks gestation. This analysis concluded that there was wide variation in the pragmatic definition of viability based on both gestational age and birth weight. These definitions have an impact on the decision to initiate respiratory support and explain some of the international variation in survival.

A second analysis compared ethical decision making in the units included in the EPICE study with the same units that were in the MOSAIC study in 2003 and explored concurrent trends in extremely preterm mortality and severe morbidity. Ten of the European regions in EPICE participated in both studies. 70 hospitals provided information on policies for the management of extremely preterm births using structured questionnaires in both of the studies and 1240 in 2003, 1293 in 2011/12 infants less than 27 weeks of GA were born in these hospitals. McNerman's Chi2 test, paired t-tests and conditional logistic regression were used for comparisons.

Between 2003 and 2012, the lowest gestational age at which maternity units reported performing a caesarean section for acute distress of a singleton non-malformed fetus decreased by one week, on average, when parents were in favour of active management (mean 24.8 to 24. 1 weeks; $p<0.001$) or against it (mean 26.1 to 25.2; $p<0.001$). Neonatologists were called more often for spontaneous deliveries starting at 22 weeks of gestation in 2012 and were more likely to make decisions about active resuscitation alone, rather than in multidisciplinary teams. Policies for withholding or withdrawing mechanical ventilation did not change. In-hospital mortality after live birth for extremely preterm infants decreased from 50% to 42% ($p<0.001$). Units reporting more active management in 2012 experienced larger declines (55% to 44%; $p<0.001$) than units where policies stayed the same (43% to 37%; $p=0.1$). Differences between periods and units persisted after adjustment for perinatal characteristics.

This analysis showed that European hospitals reported more active management of infants born before less than 27 weeks of GA in 2012 compared to 2003. The results suggest that changes in policies related to the active management of extremely preterm infants explain part of the observed mortality declines over the past decade. The observation of an effect over time lends greater credence to a potentially causal relationship between these unit policies and risk adjusted survival.

The ethics analyses were led by Mercedes Bonet, Lucy Smith and Jennifer Zeitlin

Tradeoffs beween mortality and morbidity

Advances in obstetric and neonatal care, together with more active management of infants born in the lowest gestational ages, have resulted in increasing survival after very preterm birth in high-income countries. [46 47 48] Professionals have expressed concerns about increased survival leading to higher risks of impairment among survivors, as more fragile and sicker infants survive (Lam 2009, Gallagher 2016). While older time series provided contradictory results about the potential trade-offs between mortality and morbidity, recent studies of time trends suggest that more active treatment and improved survival have not resulted in increasing proportions of major neonatal morbidity (intraventricular hemorrhage, IVH; cystic periventricular leukomalacia, cPVL; necrotizing enterocolitis, NEC; and retinopathy of prematurity, ROP) among survivors, but that broncho-pulmonary dysplasia (BPD) may increase as more fragile infants survive. [46 47 48] Nevertheless, it is unknown how changes in morbidity rates in regions with high versus low mortality would affect the absolute number of survivors with severe neonatal morbidity. Even though morbidity may stay the same, an increase in survival would lead to a greater absolute number of children with severe morbidities.

We used the data from the EPICE project to explore the potential tradeoffs between mortality and morbidity. We hypothesized that higher survival after preterm birth does not lead to increased

severe morbidity, but may be associated with an increased risk of BPD among survivors. Because our study is population-based we also sought to simulate how survival in regions with different rates of morbidity would affect the absolute numbers of survivors discharged with severe neonatal morbidity.

To test this we computed adjusted mortality rates, taking into consideration maternal characteristics (age, parity, pregnancy complications) and neonatal characteristics (sex, gestational age, small for gestational age). We then correlated the regional rates of severe morbidity (defined as above) both adjusted and unadjusted with adjusted regional mortality. No association was found. We then simulated the impact of low and high mortality and morbidity rates in our sample to assess the contribution of these two rates to the prevalence of infants discharged home with severe morbidity. We found that variations in the rates of severe morbidity had a far greater effect on the absolute number of children discharged home with morbidity than did variations in the mortality rate.

The morbidity analyses were led by Jennifer Zeitlin and Anna-Karin Edstedt-Bonamy

3.6 Use of evidence-based care in the EPICE cohort: a description

This section describes the use of several key interventions selected for study in the EPICE cohort. It is followed by summaries of the principal studies carried out on specific interventions. Each intervention has its target population and outcome measure and therefore most analyses require an intervention-specific approach. This is discussed in the impact section (4.0) of this report where the actionable messages of the project are synthesized.

Figures 6 and 8 provide data on key obstetric and neonatal interventions. The format used for the presentation of these figures is similar to Figures 4 and 5, with the cohort average in blue and the two regions with the highest and lowest values in red and green.

Administration of antenatal corticosteroids to infants in the cohort was generally high with rates above 88% among live births, on average. However, the regional range was wide: some regions managed to attain proportions nearing 100%, whereas others had rates below 80%. Given the strong proven link of corticosteroid administration with mortality and morbidity,[49] this intervention was identified early on in the study as an area for further improvement and contributed to the development of the composite measure described in the analysis section below.

Practices of caesarean section also varied greatly, including for caesareans before labour. Overall 66% of very preterm infants were delivered by caesarean, but that rate was 94% in the two regions with the highest rates versus 54% in the regions with the lowest rates. Given the lack of evidence for carrying out systematic caesareans for these children, this indicator also gives cause for concern and led to the proposal of 4 writing groups on this topic (determinants of caesarean, outcomes of caesarean for singleton non-malformed infants in a vertex position, outcomes for singleton breech deliveries and outcome for twin deliveries). As illustrated in Figure 7 which displays the caesarean delivery rate in maternity units with at least 20 births and distinguishes between regions by colour, there was a high variability of practices by unit in some of the regions.

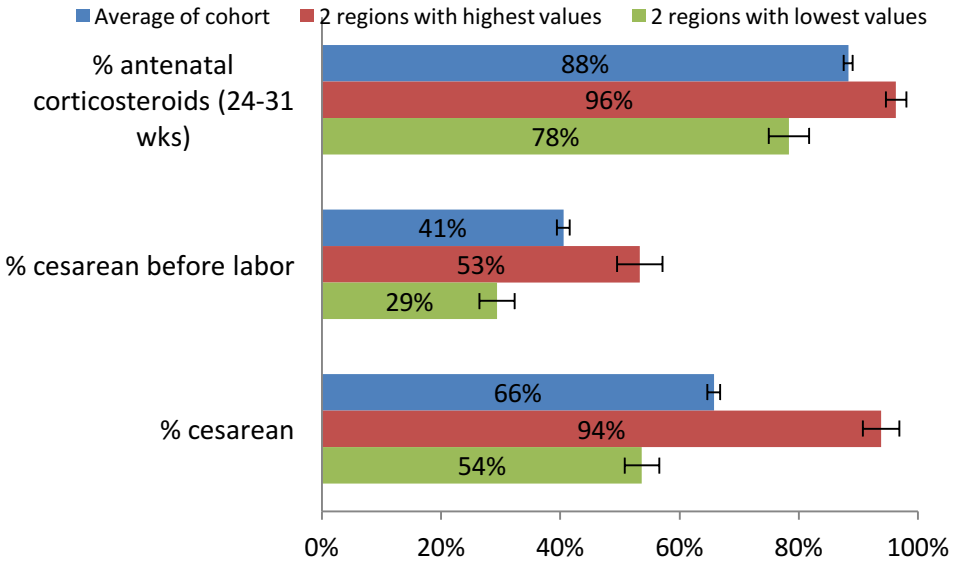

Figure 6 Variation in obstetrical interventions

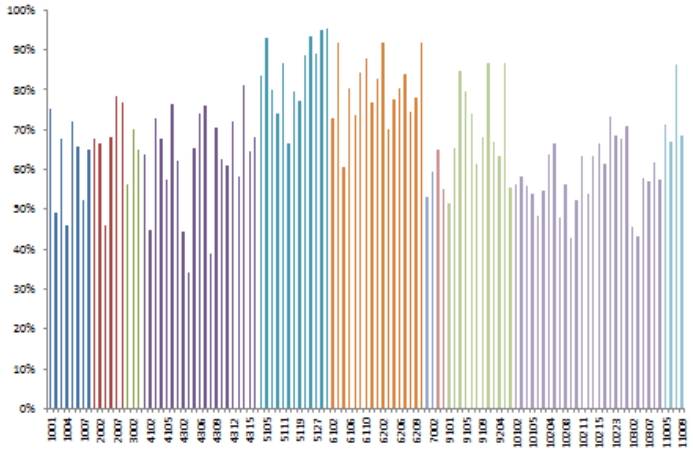

Figure 7 Percent of very preterm live births <32 weeks of GA delivered by caesarean, obstetrical units with more than 20 very preterm deliveries per year, regions presented in different colours

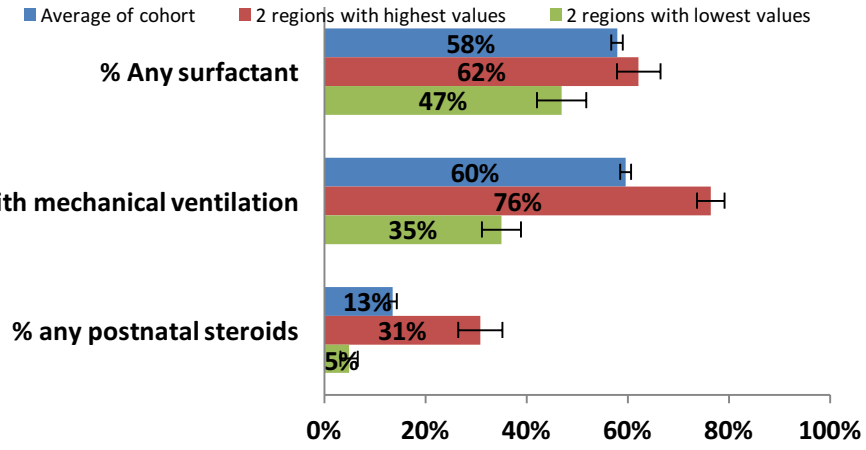

Figure 8 Variation in neonatal interventions

Figure 8 describes several key postnatal interventions. Use of surfactant was 58% in the cohort with a range from 47% to 62% in regions with lowest and highest values. A greater variation was observed for use of mechanical ventilation. While 60% of the overall cohort was mechanically ventilated, this ranged from 35% to 76% in the regions with highest and lowest values. While there were European guidelines about respiratory support in place at the time of the EPICE project, [50] our data show that these were interpreted very differently across regions. Finally systemic postnatal steroids to treat BPD were given to 13% of the cohort, but the variation across regions was very high. More in-depth analysis of this intervention is presented below.

3.7 Analyses: Determinants and outcomes of evidence-based care

Use of evidence based care and mortality and morbidity

Evidence-based (EB) practices are shown to improve preterm health outcomes in randomised trials, their use and impact in routine clinical practice remain poorly understood. We aimed to study the implementation of high-evidence practices to assess whether they constitute a lever for reducing very preterm mortality and morbidity.

The first task was to select interventions that could be used to assess short-term outcomes. We identified four with a high-level of evidence that are related to mortality and short term morbidity and that could be measured reliably using information from medical records. We then established minimum thresholds for EB care which would be accepted across all regions. Indicators were: delivery in a maternity unit with appropriate neonatal care services[50] using national level of care designations, any administration of antenatal corticosteroids (ANC) before delivery,[49] effective hypothermia prevention, defined as an admission temperature of ≥36°C which corresponds to the lower limit of current recommendations[51 52] and surfactant within two hours after birth or early nasal CPAP for infants born before 28 weeks of GA.[53 54] We computed a variable measuring the receipt of all practices given each infant's eligibility.

Infant outcomes were in-hospital mortality, severe neonatal morbidity at discharge and a composite measure of death 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.

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

The EB analysis was led by Jennifer Zeitlin and Rolf Maier.

Analyses of individual interventions I: postnatal corticosteroids

Postnatal steroids (PNS) were widely used to treat and prevent bronchopulmonary dysplasia in preterm infants until studies showed increased risk of cerebral palsy and neurodevelopmental impairment.[55 56] We described PNS use in Europe and evaluated the determinants of their use, including neonatal characteristics and adherence to evidence-based practices in neonatal intensive care units (NICUs). Our study population was 4096 infants born between 24 and 29 weeks' gestation.

We did not include babies born after 29 weeks as PNS use is very low in these infants. We analysed the risk factors associated with PNS use using logistic regression analysis and then divided the cohort into three groups by their probability of PNS use. We also evaluated the impact of the neonatal unit's reported adherence to European recommendations for respiratory management and a stated policy of reduced PNS use.

In this sample, PNS were prescribed for 13.9% of infants (regional range 3.1–49.4%) and for 29.7% of infants in the highest risk tercile (regional range 5.4–72.4%). After adjustment, predictors of PNS use were a low gestational age, small for gestational age, male sex, mechanical ventilation, use of non-steroidal anti-inflammatory drugs to treat persistent ductus arteriosus, region and a stated NICU policy of reduced PNS use (odds ratio 0.29 [95% CI 0.17; 0.50]).

This analysis concluded that PNS are frequently used in Europe, but with wide regional variation that cannot be explained by neonatal characteristics. Even for infants at highest risk for PNS use, some regions only rarely prescribed PNS. A stated policy of reduced PNS use was associated with observed practice and is recommended.

The PNS analysis was led by Alexandre Nuytten and Patrick Truffert.

Analyses of individual interventions II: Hypothermia

Heat loss after delivery holds risks for the very preterm infant. There are effective interventions, including wrapping the infant in a plastic bag, covering the head with a cap, as well as using radiant heaters and exothermic mattresses, that prevent rapid heat loss after delivery and preserve body temperature to admission for neonatal care. [57] Recent evidence has shown that placing extremely preterm infants (<28 weeks of gestation) in plastic bags or wrapping them in plastics immediately after birth, without drying, is effective to prevent hypothermia. The importance of combining several approaches for heat-loss prevention after birth, i.e., implementing a bundle of temperature preserving strategies, has been emphasized.[58]

We examined the incidence of hypothermia in the EPICE cohort and investigated the risks of death stratified by postnatal age; and major morbidity in the neonatal period. We analysed associations between body temperature at admission and in-hospital mortality, and morbidity using mixed effects generalized linear models. The final model adjusted for pregnancy complications, singleton or multiple pregnancy, antenatal steroids, mode of delivery, gestational age, infant size and sex, and Apgar score.

53.4% of the cohort had a body temperature at admission below 36.5˚C, and 12.9% below 35.5˚C. In the adjusted model, an admission temperature <35.5˚C was associated with increased mortality at postnatal ages 1 to 6 days, (risk ratio [RR]: 2.41; 95% confidence interval [CI]:1.45-4.00), and 7 to 28 days, (RR: 1.79; 95% CI: 1.15-2.78), but not after 28 days of age.

We found no associations between admission temperature and major neonatal morbidity. Admission hypothermia after very preterm birth is a significant problem in Europe, associated with an increased risk of early and late neonatal death. This analysis added to previous studies on the association between hypothermia and adverse neonatal outcomes[59] by providing recent data from Europe and by linking hypothermia to timing of death, which had not previously been done;

The hypothermia analysis was led by Emiljia Wilson (as part of her PhD thesis) and her supervisor Anna-Karin Edstedt-Bonamy)

3.8 Analyses: Effectiveness of interventions in an observational setting

Another objective of the EPICE study was to carry out comparative effectiveness research by assessing the use and impact of interventions in an observational setting. These analyses add knowledge to data from trials and raise questions for the regions involved in EPICE and for future research, more generally.

Example I: PDA

The evidence for a reduction in neonatal morbidity and improved outcome after treatment for patent ductus arteriosus (PDA) in very preterm infants has not been convincingly established. [60] This study explored the regional variation in management of PDA in very preterm infants in the EPICE cohort, its relation to case-mix and associations with bronchopulmonary dysplasia (BPD) and survival without major neonatal morbidity.

Our study population included the 7,405 infants born before 32 weeks of gestation and surviving ≥24 hours after birth. Of these, 6,896 infants (93%) had complete data on PDA-treatment (pharmacological or surgical). Our main outcomes were Bronchopulmonary dysplasia defined as oxygen treatment at 36 weeks postmenstrual age or survival without major neonatal morbidity (surgical necrotizing enterocolitis, retinopathy of prematurity ≥grade 3, intraventricular hemorrhage ≥ grade 3, cystic periventricular leucomalacia). Case-mix was compared across regions using propensity scores for PDA-treatment based on maternal and perinatal characteristics.

Between the 19 regions, the proportion of PDA-treatment varied from 10-39 % ($p<0.001$). The propensity scores for PDA-treatment could not explain the variation in treatment. Based on the distribution, regions were categorized according to low (<15%, n=6), medium (15-25%, n=9) or high (>25%, n=4) proportion of PDA-treatment. Infants treated for PDA were at higher risk of BPD in all treatment categories, with an overall propensity score adjusted risk ratio of 1.61 (95% confidence interval 1.36 – 1.91). Survival without major neonatal morbidity was not related to PDA-treatment.

PDA-treatment varies largely across different regions in Europe without associated variations in case-mix or neonatal outcome.

Example II: nCPAP

Management of respiratory distress syndrome (RDS) with nasal continuous positive airway pressure (nCPAP) is now commonly used in very preterm infants to avoid intubation and mechanical ventilation after birth as well as for weaning from mechanical ventilation to avoid reintubation. However, many infants managed initially on nasal continuous positive airway pressure subsequently require intubation and ventilation and may suffer the consequences of delayed surfactant administration. We investigated rates of failure of nCPAP and investigated risk factors for failure in the EPICE regions.

Our study population included infants without serious anomalies admitted to neonatal care (n=6582) who received initial nCPAP (n=2857). Failure was defined as mechanical ventilation in the first 72 hours. Independent variables were multiple pregnancy, pregnancy complications, prenatal corticosteroids, cesarean delivery, GA, small for gestational age, sex, 5-min Apgar, InSurE (surfactant treatment followed by immediate (30') extubation), birth to nCPAP interval and region. We used multilevel logistic regression models to account for clustering within centers and regions.

43% of infants received initial nCPAP with a range from 6.6% to 82.2% across regions; 20.1% failed nCPAP (regional range: 0% to 48.1%), with highs of 50.0% for infants <26 weeks GA and of 32.8% when Apgar was <7. After adjustment, low GA, male sex, preeclampsia, no prenatal steroids,

prelabor cesarean and Apgar <7 were associated with failure while preterm premature rupture of membranes was associated with lower failure rates. Region was associated with failure rates after adjustment for patient characteristics.

This study confirmed the impact of known risk factors for nCPAP failure, such as low gestational age and male sex, and identified new risk factors: pre-eclampsia, eclampsia and HELLP, cesarean section before labor, lack of antenatal steroids and an Apgar score <7. These results provide information for clinicians making decisions about initial nCPAP and raise important questions for further research on the determinants of respiratory disease and its underlying mechanisms. In addition to these perinatal factors, region was associated with nCPAP. This result indicates that use of nCPAP may also depend on the training and experience of the staff or on staffing levels in units and suggest that quality initiatives could improve nCPAP success.

Example III: Breastfeeding and unit parental policies

Breastfeeding a very preterm infant is challenging, but the rewards may be substantial. [61] Maternal milk confers protection against infections and necrotiziong enterocolitis [62] and promotes brain growth, neurodevelopment and possibly cognitive function [63 64] Several maternal characteristics such as age, ethnicity, smoking and socio-economic factors are known to be associated with initiation and duration of breastfeeding. However, these variables are not in themselves amenable to intervention by the perinatal health care services. In search of modifiable factors, we explored the impact of neonatal unit policies towards presence on use of maternal milk and breastfeeding in the NICU.

Using variables present in the neonatal unit questionnaire, including the number of hours parents could enter the intensive care area over the 24hr, maximum allowed visit duration, whether they can stay during medical rounds and spend the night in the unit, we built a “visiting score” (range 0-10, with higher values indicating more liberal policies). After adjusting in multivariable analysis for unit level, dedicated staff to support breastfeeding, use of protocols to promote breastfeeding and developmental care and kangaroo care offer to mothers and fathers, we found that babies cared for in units with more liberal visiting policies were about two-fold more likely to receive exclusive maternal milk at initial feedings and at discharge from hospital. These findings were statistically significant. Routine offer of kangaroo care to fathers was a strong predictor of exclusive maternal milk feeding within the first 3 days of life (aOR 5.7, 95% CI 1.5-22.0) and in the 24 hr following the first enteral feed (aOR 6.2, 95% CI 1.6-26.1), while no effect was noted at discharge.

Breastfeeding at discharge from NICU, either exclusive or mixed, was associated with a policy of routine offer of Kangaroo care to mothers (aOR 2.4, 95% CI 1.0-6.1). Additionally, having a protocol for developmental care (but not for breastfeeding and use of maternal milk) was a significant predictor of exclusive use of maternal milk at initial enteral feedings and feeding at the breast at discharge.

A modification of neonatal units policies to make care more family-centred may be a cost- effective way to increase brestfeeding rates in very preterm infants.

3.9 From knowledge to change: the qualitative studies

Knowledge is available on how protocols and clinical guidelines should be developed and updated, adapted for local use, implemented and evaluated. Also, a lot of work has been performed on the evaluation of strategies aiming to increase the likelihood of protocols uptake by clinicians [19 65] and to effectively promote change. However, it is not known to which extent this knowledge is applied in practice, and whether the steps that have been proposed in the literature to inform, involve, and support clinicians are carried out. Indeed, the low uptake of evidence-based guidelines and resistance to change highlighted by many studies [20 66 67] may in part be due to inadequate implementation of the available scientific knowledge about the processes of change.

While quantitative studies such as the EPICE cohort project are essential for documenting differences in use of interventions and policies, and identifying associations with factors at the patient and unit levels, qualitative methods are necessary for a more in-depth understanding of the decision-making processes and of the health care professionals attitudes and feelings. Such understanding is important for refining the conceptual models that underpin the promotion of behavioural change. Thus, the EPICE qualitative study was focused on the decision-making process for the development, implementation and evaluation of clinical protocols and/or guidelines in neonatal intensive care units based on the most recent change that occurred to unit clinical guidelines or policies.

The objectives of the qualitative study were to:

- Explore the experiences, practices and attitudes of different neonatal health care professionals (medical and nursing background) as regards the development, implementation and use of clinical guidelines and protocols, in order to reach a better understanding of the facilitators and barriers to their use in the different European regions.
- Explore the interplay between the interdisciplinary communication patterns emerging from the qualitative interviews and the units' organisation and policies and clinicians' practices documented by the Unit and cohort studies.
- Apply the findings of the qualitative study to the analysis and interpretation of the quantitative study results, in order to develop more specific strategies aimed at modifying the clinicians' behaviours and units' policies.

The focus on the process of change (reasons, planning and implementation, barriers, facilitators) rather than on specific interventions allowed all regions that wished to participate to do so, as the interview content was not contingent on use of a particular intervention; additionally, it allowed us to start linking qualitative data with structured data from the unit questionnaires regarding the unit's characteristics and reliance on evidence for protocol development.

We asked informants to report on the last change in policies or practices introduced in their unit. This choice of discussing a real experience was aimed at obtaining an overview of the type of changes recently taking place in European NICUs, and also to avoid theoretical discussions and generic statements. Consistently, the interview guide was built according to a chronological order -from planning and development to implementation and assessment- in order to provide a framework that would help to structure the discussion and facilitate memory.

The study was carried out in one large region per country with the local resources to perform the interviews: Denmark (Eastern region), France (Ile-de-France), Germany (Hesse), Italy (Lazio), Portugal (Northern), and UK (East Midlands). Only third level Neonatal Intensive Care Units (NICUs) were eligible. Units where members of EPICE Steering committee are based were excluded.
In every region, two tertiary NICUs were randomly selected by the INSERM coordinating centre, with stratification for academic status, and invited to participate. We aimed at interviewing 4 staff members (2 physicians and 2 nurses) in each participating unit, using the following criteria (1)priority given to staff members who were reference persons for development of protocols and guidelines, or who were most knowledgeable about these issues; (2) at least 3 years of experience in neonatal intensive care in the Unit where the study is taking place (binding criterion). The Unit chief and head nurses might also be interviewed. Deputies were interviewed only in case they replaced the Unit head and chief nurse. There were no explicit refusals; however in Denmark only one unit participated. The other unit did not refuse, but multiple scheduling problems made it impossible to carry out the interviews within the study period. Overall, 42 staff interviews were carried out.

Table 12 lists the topics that were selected by the doctors and nurses who were interviewed.

Table 11 List of topics selected for the qualitative surveys

Proposed by physicians	Proposed by nurses
Ventilation (n.8): • Initial infant stabilization through non-invasive ventilation • Introduction of Targeted Tidal Volume (TTV) ventilation • Use of humidified High Flow Nasal Cannula • Introduction of Optiflow/High-flow nasal cannula oxygen • Use of RAM cannulas for PPC • Setting of oxygen saturation limits • Change of saturation targets to 90-95 • Protocol for improvement of trainees' intubation skills Enteral Feeding (n.4): • Change of feeding schedule (n.2) • Feeding with raw and customized milk since 28 weeks gestation • Use of fresh maternal milk (versus frozen) Infant Care (n.3): • Development of protocol for Kangaroo care • Assessment and prescription on the basis of pain measurement scales • Transfer from incubator to open cot Parental nutrition (n.2) • Early parental nutrition bag (first day) • Request of parental nutrition bags in anticipation, according to the predictable baby's weight Neonatal infections (n.2): • Implementation of NICE guidelines for Neonatal Sepsis • Written regimen for vancomycin dosing Others (n.2): • PDA closure • Guideline of local silver nitrate application for the treatment of umbilical granuloma	Infant Care (n.7): • Establishment of the Kangaroo care method (n.2) • Guidelines for neonatal pain management • Infant bathing schedule • Introduction of kinaesthetic infant handling • Policy towards parents • Review of discharge procedure for the Neonatal Unit Ventilation (n.5): • Use of new fastening system for ventilation • Guidelines for adjusting neopuff settings according to ventilator settings • Introduction of a guideline for difficult intubation. • Introduction of Targeted Tidal Volume (TTV) ventilation • Use of apnea sensors to adapt ventilation pressure Others (n.5): • Management of umbilical catheter • Heart disease screening: pre-ductal and post-ductal saturation (at arrival and in the 3rd/4th day) • Regular (TID) check-up/technical examination of the resuscitation unit equipment • Change of caffeine citrate mixing and administration • Introduction of NICE guidelines on phototherapy Use of fresh maternal milk (n.4): • Initiate use of fresh maternal milk (n.2) Gemelli) • Feeding with raw and customised milk since 28 weeks gestation (n. 2)

With informants' permission, the interviews were anonymously recorded and transcribed "verbatim". Text coding was carried out according to a coding scheme developed by the study group. Further analysis included searching for "themes", or patterns across the data set that are important to the description of a phenomenon, and are associated to specific research questions **(**Guest G. Applied thematic analysis. Sage Publications 2012: Thousand Oaks, California.

This study is described in the final report submitted as Deliverable 5.1. The following section summarizes these principal themes.

Our results open a window on to what induces and motivates change in neonatal intensive care. The need to standardize patient management and improve care was reported as a major determinant of the development or updating of Unit policies and prococols. New findings in the literature, information and knowledge acquired through participation in meetings or informal discussions with colleagues from other units, and also reaction to adverse events occurring in the Unit represent other key triggers for change.

Table 12 Main themes that emerged from the qualitative analyses

Main Themes	Sub-themes
1. Introduction of new guideline/policy: reasons and triggers for change	1.1 Need to standardize practices 1.2 Newly issued guidelines to be adapted 1.3 New information from the literature, scientific meetings, and colleagues 1.4 Improve patient care 1.5 Other reasons
2. Barriers and difficulties encountered	2.1 Seeking agreement 2.2 Time, resources and workload 2.3 Communication and dissemination difficulties 2.4 People attitudes and resistance to change 2.5 Poor quality of the evidence
3. Facilitators	3.1 Quality of the guideline 3.2 Perceived benefit to patients 3.3 Perceived benefit to staff work 3.4 Personal involvement and motivation 3.5 "Bottom-up" decision to change 3.6 Key person facilitating the process

In some countries most guidelines appeared to be produce by external bodies, such a NICE in the UK, and the unit contribution mainly consists in adapting them to the local situation, and applying them. In other countries, such as Italy and Portugal, new policies and guidelines were often the result of a sort of "bottom-up" decision to change that arose from the staff everyday clinical experience, and was motivated by the need to facilitate their own work and improve patient care. Changes initiated within the unit may concern apparently minor or very specific issues, that however can have significant consequences in terms of better wellbeing of patients and easier staff work. As they are the result of the staff reflection on their own practices, they appear to bring more satisfaction than the receipt of external professionally prepared guidelines.

In both cases, however, finding agreement within the unit team was reported as a major challenge, requiring several meetings and sometimes heated discussions. The process appeared more difficult when the evidence-base of the new guideline was not considered very strong (see Table 12); for guidelines imposed from outside the NICU, either by an official agency or by the hospital direction; and when the unit was run by several peers rather than by a single "chief". Often, full agreement proved impossible to achieve, and consensus by the majority was used. However in this case the likelihood of non-compliance seemed to increase, either without explicit justification or justified on the grounds of personal clinical judgement.

Other factors reported as undermining implementation and compliance were lack of training –when this was required for implementation, as was the case with new equipment or tasks-, inadequate staffing, and the fact that new protocols often involved a permanent increase of workload –because of the additional procedures and tasks that were prescribed- without increase of staff.
Together with being convincingly evidence-based, other features that facilitated the uptake of guidelines and led to stable behavioural change were mentioned. The quality of the guideline itself is very important. According to our informants, it is important that a guideline is unambiguous, clearly written and easy to interpret. It should be practical, with clear explicit aims. Unnecessary length and too much theoretical background and details ("all the sort of bits that nobody reads") should be avoided. Guidelines that smooth out the staff work are very much appreciated and very likely to be followed. When a guideline entails new tasks and increased workload, an evident and significant benefit to the patients or families is required. Particularly when the evidence base for a guideline is

not very strong, clinicians appreciate a certain degree of flexibility that recognizes the value of their professional judgement and allows them to take into account the specific characteristics of the patients and of the circumstances.

Table 13: Citations about the quality of evidence

Resistance to change may by fostered by a belief that the evidence base is not strong enough

- "So one of the difficulties with these guidelines is that they come out with a government stamp on them saying you must do it and you must audit them. But actually sometimes the evidence base for which the guideline is based on, is quite weak. And ultimately it comes down to expert opinion. […] Actually I think, getting buy in from the whole team can be difficult, particularly when the evidence isn't strong. […] Because trying to be enthusiastic and saying 'we really must do this', when you're thinking 'must we?' [Smiling], is… is quite hard ". (Phys/UK/2)

- This type of resistance may be in place also when doubts between the level of evidence are ill-founded: "That means, if people are not really convinced about the benefit of breastfeeding, it is even more difficult and even less motivating to do all this, which takes time, energy... ". (Nurse/Fr/3)

- So I do think that… you know, particularly if it's evidence-based, then people are much happier to have evidence-based change. Uhm if you want to work, you know, people are happy to work to a national level if it's… if it's evidence-based that that's the best practice. Nobody would want to go against that I don't think. […] Uhm well because a) it's far more accurate than what we used to do [laughing] and because we're working to national standards". (Nurse/UK/5)

Overall, the interest of the patient and /or the parents appears to be a major factor driving change for the majority of professionals. The wish to improve care and babies wellbeing leads to the identification of areas in need of improvement, to the development and discussion of new policies, and ultimately to compliance and actual behavioural change (see Table 13). Even small changes that appear to improve patient wellbeing and prevent adverse events are considered important and are a real source of satisfaction for the staff.

Table 14: Citations about the interests of the patients or parents

The interest of the patient or the parents are a major factor driving change

- "Then, as long as people understand that the change is in the interest of the child it is not just to change the way we think …So, there is no reason not to comply with the protocol" (Nurse/Fr/3)

- Commenting the recent introduction of the use of standardized pain scales, the informant said: "People understood the importance and stopped saying 'what a bore, we have to do this' and even for attending the training sessions there had to be encouragement and explanation that it was important and that, and that the success of this project could bring enormous benefits for the babies […]. Even with venipuncture and so on, whenever possible the mother [has the baby] in the Kangaroo position, and there is, you see a decrease [in level of pain], because we have the levels of pain on a scale. And we can be objective about the decreases which we couldn't do before, of pain right? We feel this is very beneficial." (Phys/Port/1)

- About the use of maternal milk: "And then eventually we saw that the growth of babies… less intolerance, less NEC, at the end you see a result on the babies you care for, and therefore you can see the advantage. You are more keen to comply". (Nurse/It/5)

There is, however, a balance to be maintained between workload, time and resources, as well as a need to feel that the clinicians' role and autonomy are respected and valued. Guidelines issued by external agencies, as opposed to those prepared by scientific societies or originated within the units, are perceived as more likely to neglect these principles.

The qualitative analyses were led by Marina Cuttini and Emanuela Forcella

4. Impact and dissemination

4.1 Actionable messages

Carefully conducted and analysed research can save lives by helping decision makers design effective policies and programs. For research to influence policy, however, it needs to be communicated effectively and used in the decision-making process.

- ***The research literature strongly suggests that research organizations should transfer actionable messages from a body of research knowledge, not simply a single research report or the results of a single study. Research on managerial and policy decision making has taught us that research in the form of "ideas" not "data" most influences decision makin.***

This principle is highly relevant for the EPICE study:

- EPICE has produced results that cover many diverse areas of clinical practice.
- It would not be feasible to try to incorporate each of these findings into clinical practice, particularly given the diversity of the environments in which neonatal care is delivered.

Therefore, we needed to identify overarching messages that can provide information and support to lead to change. The key messages were identified based on the results from the analyses using EPICE data and discussions and written input provided by the EPICE research group. These messages provide a framework for the dissemination activities. We identified 7 principal actionable messages.

1. Evidence-based practices are under-used and affect mortality and morbidity.
    - Use of evidence-based practices impacts mortality and morbidity.
    - Units that employ evidence based principles and practice have lower mortality rates.
    - The practices that have been the focus of the EPICE study are those that have previously been subjected to investigation with randomised controlled trials and have been shown to be effective.
    - We have now shown that these same practices also appear to be effective in unselected, "real life" environments, where many other practices differ.
    - These practices are underused, so there is a possibility of achieving substantial changes by improving adherence to evidence-based care.
2. Mortality and morbidity are high for very preterm infants and it is a continued imperative to improve their health outcomes.
    - Intact survival for very preterm infants needs to be improved.
    - There are substantial lifetime costs and thus important potential gains.
    - Large variability across regions, not explained by maternal or infant characteristics.
    - Benchmarking also revealed high variability across units.

3. The organisation of health care services and systems has an impact on health outcomes for very preterm infants. Messages regarding organisation of care are region-specific in their importance.

   - Delivery out of specialized units (ie units without any neonatal intensive care) is associated with higher mortality AND morbidity. This message is relevant for countries where very preterm infants are delivered in level I units, for instance, France and Poland.

   - Being born and hospitalised in smaller units, even with an onsite neonatal ward, is associated with a higher mortality. This is of relevance in: Portugal, Germany, Italy where many infants are born and hospitalised in units with a low annual case volume.

   - Neonatal transport should be avoided. This relates to the two points above and also, in Estonia, to the location of intensive care services in paediatric hospitals which are geographically separate from the specialised maternity units.

   - Overall, organisational factors had an impact on receipt of evidence-based interventions as measured by the All-or-None composite developed for the EPICE study. Therefore national, regional or local policies to improve receipt of these practices must be based on an assessment of the organisational obstacles within their health system in addition to those affecting practices within the units themselves.

4. There are many areas where consensus on best-practice appears to be lacking and where guidance for clinicians should be improved.

   - There is an absence of standardized protocols and guidelines for many practices on national, regional and unit levels, even when these are backed by solid evidence.

   - The evidence-base for many of the interventions frequently used for the care of very preterm infants is unclear; Guidance from professional organisations could make it easier for front-line clinicians to develop protocols and standardise care.

   - The observational data revealed multiple examples of wide variation in practice in the care of very preterm infants: Complex conditions with large variations in management would likely benefit from increased standardisation to improve care (examples are patent ductus arteriosus (PDA) or use of caesarean delivery).

5. Decisions to initiate active management at very early gestational ages remain an important determinant of mortality and of differences in mortality between countries.

   - Attitudes and beliefs about the benefits of initiating active management for infants born at very early gestational ages need to be considered in order to understand differences in mortality between countries.

   - Ethical decision-making needs to be addressed for the successful implementation of change.

   - A tradeoff between a lower mortality rate and higher morbidity was not observed in our data, confirming recent studies showing that declining mortality is not accompanies by higher neonatal morbidity. What made the most difference in terms of children at risk for impairment was attaining a low morbidity rate. These messages are important to relay to clinicians for focusing on improving care for these infants.

   - Follow-up of these children to childhood is needed to provide complete data on their health, development and quality of life.

6. High-quality research on the effectiveness of interventions is a powerful agent for change. This evidence should come from interventional trials as well as observational studies.

   - The EPICE qualitative study illustrated the importance of having convincing evidence of effectiveness in order to motivate clinicians to adopt new protocols and practices. Interviews with personnel showed that change often involves considerable additional (and unremunerated) effort and therefore staff buy-in is indispensable. A key facilitator for this extra effort was whether the personnel were convinced by the evidence. High quality evidence on the effectiveness of specific interventions is generated from well-designed randomised trials.

   - The other key motivator for personnel was the impact of change on the very preterm infants and families in their care. This finding underscores the importance of collecting and analysing data on the effectiveness of interventions and the improvements of patient outcomes in routine clinical settings. Observational studies, such as those carried out in EPICE, but also analysis of data collected by neonatal registers or other hospital data, are an essential component of the evidence-base.

7. All European regions can improve the care provided for very preterm infants. Although the areas of most relevance differ by region, the same obstacles are present everywhere.

   - While we expected to find very different approaches to the implementation of new knowledge across the European regions, the results of the qualitative studies showed that barriers and facilitators to change were very similar in European neonatal units.

   - Despite all the variety and differences which emerged from our results: no region emerged as "the best" or "the worst" on all the dimensions of outcome and practices considered. Every region was able to identify areas where improvements were necessary.

4.2 The European dimension and region-specific impact assessments

By undertaking the studies in 19 European regions, we increased the heterogeneity of organisational, social and cultural contexts and maximised the variability in the interventions studied. This made it possible to capture the multiple approaches to perinatal care today and to raise questions about the determinants of decision-making and the consequences of these different practices. Yet, it also adds complexity and requires input from within each system. The conceptual models and intervention strategies that have been built from the EPICE study results are based on associations that hold true in a wide range of organisational and cultural environments. This fact adds to the external validity of its findings. However, these then need to be filtered through the political, cultural and organisational context in each region.

The following provides some of the research results which were found to be relevant by the regional teams. This table covers only one or two points per country to illustrate the range of themes that have been flagged as relevant and is not intended to be comprehensive or to reflect a priority ranking. The full regional impact assessment identified multiple action points per region and is used by the writing groups to make the dissemination messages and materials more meaningful (see 4.3 below).

Table 15 Region specific comments on key results

(Region) Country	Comments and selected salient impact points
(Flanders) Belgium	It's the impression that many NICU's in Flanders still frequently use NSAID's for treatment of PDA. The EPICE analyses shed more light on this matter, supported with the data from the present literature. There is, In general, insufficient documentation of temperature on admission which concerns most likely also late preterm and term neonates admitted to NICU's in Flanders and should be explored. EPICE data supports this need
(Eastern Region) Denmark	Regionalization has been a focus in Denmark during the last 20 years. A debate in Denmark concerns specialty plans and centralization. The data obtained in EPICE provides useful information to support the process that in the end is a political decision. Denmark has a tradition of using CPAP in very preterm infants. The outcome varies greatly between the European countries and the EPICE study allows us to analyse the use of CPAP and its impact in very preterm infants
Estonia	The results are relevant for Estonia because we (our hospitals) don't belong to any International register (Vermont-Oxford or Euroneonet) and collection of statistics for the Medical Birth register is limited with 7 postnatal days. Therefore the data collected and information gained is important for both clinicians and policy makers to generate awareness; also to review the current strategies; for creating new guidelines; find good practices and identify hospital with good practices.
(Ile-de-France, Burgundy, Northern Region) France	The EPICE results suggested that there are large differences in active management in cases of extremely preterm birth between France and other European countries. This has led to a discussion among clinicians about current guidelines. Further, use of antenatal steroids is lower in France than in some other countries, which may be one consequence of more conservative management.
(Hesse and Saarland) Germany	Germany is different from other European countries in relation to the organisation of care: There are about 200 Level III units for about 680 000 births per year. Mean number of infants < 1500 g less than 50 per unit. The EPICE results are therefore relevant for policy makers. Germany has a very high caesarean section rate compared to other European countries. This is relevant for clinicians and provides data to show that current practices are not all evidence-based.
(Lazio, Emilia-Romania, Marche) Italy	Italy is different from other regions in having more restrictive rules for parental visiting. The EPICE project has provided us with the opportunity to compare Italian unit policies to policies elsewhere and to analyse the impact that this has on breastfeeding.
(Central and Eastern regions) Netherlands	Variations in mortality Currently subject of study in teh netherlands looking at variation between the 10 Dutch centres. Relevant for professionals. Postnatal corticosteroids There is a multicentre study going on in the Netherlands/Belgium (STOP BPD) looking at second week treatment of hydrocortisone versus placebo. Relevant for professionals
(Wielkopolska) Poland	The most relevance in Wielkopolska region related to perinatal factors influencing neonatal mortality and morbidity is the lower number of terminations of pregnancy and overall higher number of congenital anomalies. MOSAIC and now EPICE are the first international projects which showed clearly that phenomenon, which is not widely known. The lower rate of TOP is clearly related to ethical decisions and influences the mortality and morbidity data. This situation has relevance for policy makers, which should prompt them to create a fast postnatal genetic diagnostic program allowing for efficient and rapid genetic diagnosis. Wielkopolska has also the lowest rates of antenatal steroids among EPICE participants. This situation could influence neonatal mortality and morbidity.

(Region) Country	Comments and selected salient impact points
(Lisbon and NorthernRegion) Portugal	Caesarean section is a major Portuguese issue at all levels. Large unit variation and lack of guidance regarding VPT babies. Length of stay in hospital is an issue of importance for managers and doctors. There is a large debate regarding post-hospital care and the role of NGOs and parents associations.
(Stockholm region)Sweden	Our role as leaders of the hypothermia theme in EPICE led us to understand that this is an area of improvement also in Stockholm, and perhaps all over Sweden. Our PhD-student has repeatedly presented the EPICE-data at local meetings and was first met with surprise, and sometimes disbelief. Progressively, it has been accepted that we need to improve our thermal care of the very preterm infants in the delivery room and that it is not acceptable that the risk of mortality is doubled in very preterm infants having a body temperature below 35.5 degrees C. The admission temperature is now measured as a quality indicator at the Karolinska Hospital.
(East midlands, Norther, Yorkshire and Humber) United Kingdom	Variations in very preterm mortality is a key theme for the UK as a whole as there are wide between regions and between hospital variations in mortality. The national MBRRACE-UK programme of work is designed to reduce stillbirths and neonatal mortality and investigating why these variations arise. Major issues are deprivation, ethnic differences and variation in the recording of live births around the period of viability (<24 weeks gestation). The EPICE data provides additional insight into the proportion of mortality that is affected by explanatory risk factors pointing towards areas where quality of care provision needs further investigation. Data from this analysis can be used in the development of confidential enquiries for the nation programme. This is an issue for both policy makers and care providers. Breastfeeding is major topic area for the UK where breastfeeding rates are low – especially in very preterm infants. Data from EPICE / MOSAIC can be used to inform units. This is an issue for both policy makers and care providers.

4.3 Channels for dissemination and intervention

4.3.1 Scientific publications and post-publication promotion

The EPICE project consists principally of an epidemiological cohort study exploring the use of evidence based medicine for very preterm infants. Consquently, in line with the standards and rules for dissemination of reseach findings, it's principal dissemination channel is publication in peer-reviewed scientific journals. This permits review and validation of its findings by external experts, makes results readily available in research databases and affirms ownership of this intellectual property by the authors and the EPICE project, more generally. Media strategies are also contingent on the availability of published results. The first pillar of our dissemination and intervention strategy is therefore to concentrate on the analysis of our data for publication. This process makes it possible to refine the key messages. The articles ready for publication or nearing completion at the end of the project, as well as on-going analyses have been submitted as Deliverable 7.2.

The group also developed a **post-publication promotion strategy**. We acknowledge that those with the greatest interest in evidence-based medicine are the most likely to read our papers and those less familiar with evidence-based principles are less likely. The components of this strategy are the following:

1. Publications should be open access, whenever possible. We hope to be able to use the OpenAIRE post-grant pilot project which allows for up to three post-project open access publications. Other funds will also be mobilized whenever possible for open access journals or to purchase open access rights from traditional print journals.
2. Using the network of press offices established at the beginning of the EPICE project, a press release will be discussed with the first and last authors' institution.

3. Each first and last author of every paper prepares a lay summary of the paper with the findings and the main messages. These key findings will be related to the actionable messages identified during the project and described above.
4. The lay summary and publication will be available on our website. An email will inform key stakeholders (including the involved units as well as others for which names and emails were collected during the project) about the publication with a link to the website where we will include the lay summary and information for accessing the publication. These stakeholders include people in the key medical organisations in each country. Individual regions will have the option of producing a lay summary in their own language.

4.3.2 Presentations in international scientific conferences and the stakeholder's workshop

During the EPICE project, the results have been presented in over 60 international, national and regional scientific conferences (see Deliverable 7.2). The principal messages of the EPICE project are aimed at clinicians or other stakeholders involved in the interpretation and use of scientific knowledge for policy. Scientific conferences are an ideal arena for reaching this group of experts. This strategy has allowed us to generate debates as part of the presentations, but also to network and discuss informally with opinion leaders. It has also been possible to disseminate the study results to multiple disciplines: obstetrics, paediatrics, health services research, epidemiology and to attain a broad geographic scope.

To support these presentations, the EPICE team produced slide sets showing consolidated results by region, to be used for national/regional presentations, both in scientific and organizational/political events. These slides were modifiable and changes could be requested depending on the event. These were also used for presentations in local fora (see next point). These presentations were available on the members' only section of the website.

A major part of our dissemination strategy was a daylong ***Stakeholder Dissemination Workshop***, held as a precongress event at the European Academy of Paediatric Societies in Barcelona in October 2014. Key stakeholders from within and outside of participating regions presented and discussed the preliminary results of the EPICE project, their implications and interventions that could be developed. The workshop was divided into two parts: a morning session entitled "Current practices for the care of very preterm infants in 19 European regions: on-going analyses and preliminary results" to which we invited members from the EPICE regions and selected external participants to discuss confidential, on-going analyses and an afternoon session entitled "Evidence-based care for very preterm infants: moving from research to practice" which was open to all participants in the EAPS meeting and which included a round table organized with the EuroNeoNet Network. The precongress event was provided without additional costs to all interested participants. We selected this venue as the EAPS is the principal European scientific meeting for paediatrics and neonatology. We disseminated information about the meeting directly to people speaking at the meeting, identified from the programme, from the countries included in the EPICE project as well as clinicians from other countries working on similar themes.

For the daylong workshop (morning and afternoon sessions), we invited discussants from participating regions who were not directly involved in the EPICE project and in particular: Sam Oddie and Kate Blake from the UK, Harald Ehrhardt from Germany, Chiara Locatelli from Italy, Krzysztof Szymanowski from Poland and Ana Melo Bento from Portugal. These invited guests were selected by each region because of their expertise in the care of very preterm infants and their connection with local units. They reviewed the presentations and provided an external viewpoint on our analyses and the results. Two experts from external advisory board were also able to attend: Stavros Petrou (UK) and Petr Velebil (Czech Republic). We also invited members of the the European

Foundation for the Care of Newborn Infants (EFCNI) to represent its network of parent organisations. The EFCNI has an existing extensive network of policy and stakeholder contacts at the European level and through the partnering parent associations also at national level within the EU countries. This contact at the workshop enabled us to reinforce our partnership with this organisation. Finally, we invited members of the EuroNeoNet project to participate in the workshop. The participation of the members of this group made it possible to discuss the dissemination of the EPICE indicators and continued evaluation of use of evidence-based practices in Europe, as well as the interventions needed to promote evidence-based care

4.3.2 Dialogue with clinicians, policy-makers and parents on the regional level

Another pillar of the dissemination and intervention strategy has been to present results to clinicians and policy makers within the regions and to generate debate about their relevance for clinical care and policy. During the project, multiple formal and informal meetings have been organised by regional teams to provide feedback on the project. Some of these have taken place as part of national or regional conferences, whereas others have been smaller meetings with clinicians or policy makers.

Regions have also engaged in outreach using other dissemination materials including newsletters to participating units and parents. These are described in the dissemination part of the final report and have been attached with past reports.

4.3.2 Training and action-research

Training and action research are a part of our dissemination and intervention strategy. Training early stage researchers in data analysis contributes to publications and presentations, transfers valuable skills to a next generation of researchers and clinicians and builds European research capacity. This also provides added value to the regions participating in the project. During the project, three students (one statistician, one public health researcher and one neonatologist) have completed their master's degrees using the EPICE data and 1 midwife is in the process of completing a doctoral degree. Three other students (one neonatologist, one obstetrician and one epidemiologist) are starting doctoral programmes using the data in EPICE.

The EPICE project involved clinicians in all components of the research process: conception, design, validation, data analysis and interpretation. This input is important for the validity of the findings, but also involves those most concerned with the topics under study, in line with their interests and expertise. It contributes to the transfer of skills and knowledge within the EPICE group. Over the course of the project, 23 meetings were held at which analyses were presented and discussed. Transfer of skills and knowledge within the EPICE consortium was promoted through a methods workshop about the methodological issues brought up by the analyses of the EPICE data. This workshop was organised by Brad Manktelow (ULEIC) and Aurélie Piedvache (INSERM) and established guidelines for analyses of the EPICE datasets. Topics covered were directed acyclic graphs (DAG) for covariable selection, choice of principal outcome measure (odds ratio, risk ratio, risk difference), assessment and treatment of missing data (imputation or list wise deletion of data) and methods for validating models.

4.3 Evaluation and assessment tools

4.3.1 Instruments, indicators and references

The EPICE project has developed protocols and research methods that can be used to evaluate and assess care across EU countries. These include the questionnaires for data abstraction from medical charts and the questionnaires for units. These instruments are available in multiple languages and

have been designed to be easy to understand and applicable in a wide range of settings. The research methods used for the qualitative studies are also innovative and relevant for future studies across Europe. We used a mixed approach based on trained local qualitative researchers who undertook first coding that could be translated and interpreted by the main analysis team.

The instrument used in the EPICE study to assess outcomes at 2 provides a first step towards a common validated approach to parental assessment of very preterm health and development which could work across countries. In several of the regions, Bayley assessments were also available on the children and a follow-up project is currently undertake further analyses to validate these questionnaires using these data. The Horizon 2020 SHIPS project (see below) will also make it possible to validate its predictive accuracy with respect to developmental data when the children are 5 years of age.

Other tools: indicators and references

The EPICE analyses developed a series of indicators for measuring outcomes and use of interventions in a comparative way. These include indicators of severe morbidity as well as of neurodevelopment at 2 years of age. The All-or-None composite developed to measure use of evidence-based practice can also be used to assess EB practices in other datasets. We are currently discussing implementing this indicator with regional neonatal networks.

Although this was not one of the initial topics of the EPICE project, during the analysis the issue of how to define growth restriction in our multinational sample arose. The development of suitable growth curves is currently a focus of international attention, in light of the WHO Intergrowth 21st project. We thus used this cohort to contribute to this debate and to develop tools specifically related to the population of very preterm births. These references are an important tool for future comparative studies in Europe and the promotion of evidence-based growth monitoring.

4.3.2 The EPICE cohort of very preterm infants

In addition to being one of the major achievements of this project, The EPICE cohort – the first European cohort of very preterm infants – represents a tool for continued dissemination and intervention on the topic of evidence based medicine. As the project ends, there are multiple follow-on analyses continuing on the use of interventions as members of the EPICE research group explore new questions and research hypotheses that were raised during the project.

Furthermore, the EPICE group successfully bid for a Horizon2020 project to follow-up the EPICE cohort. This project will make it possible to explore many of the themes studied in the neonatal or early childhood period in later childhood. How perinatal outcomes and interventions continue to influence outcomes is an important area of study and one in which very little comparative European data exist.

This new project, called SHIPS (Screening for Health in very Preterm InfantS) builds on one of the programmatic areas identified by EPICE and which emerged during the project as a crucial area for ensuring better care of these infants as well as a better understanding of the effectiveness of perinatal care. Follow-up screening and prevention programmes aim to identify health problems early, enable interventions to improve outcome and to allow optimal management of health care. Despite the recognised importance of these programmes, little is known about their actual application and impact. Our analyses of the EPICE data revealed high variability in current approaches suggesting that a clear evidence-base does not exist to guide programme decisions. Preliminary data showed a large heterogeneity in programme organisation and coverage.

The new project, SHIPS (Screening for Health In very Preterm InfantS) will assess the impact of these screening programmes on health, care and quality of life for very preterm infants and their families as well as on coverage, ability to meet needs, health equity and costs at the population-level. It will also generate new knowledge about assessment tools and methods and contribute to evidence-based care for this population. The SHIPS project began in September 2015.

This cohort of over 6500 infants which will be followed-up until 5 years of age constitutes a unique resource for generating knowledge about the effectiveness of antenatal care, delivery, neonatal and post discharge care and the needs of these children and their families. This new project with financing to keep the cohort open will reinforce this knowledge platform and make it possible to get information in future projects on the longer term impact of health care provision at birth and in the first 5 years of life for very preterm infants. Life course epidemiology is now recognised to be an indispensable tool for understanding child and adult health. This cohort thus represents an opportunity, if continued funding can be obtained, to follow-up very preterm infants into later childhood, adolescence and adulthood.

5. Address of project website and contact details (no limit)

www.epiceproject.eu

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