Perinatal care at the threshold of viability

Part I: Systematic Analysis of Outcomes and Resource Needs for Neonatal Intensive Care Units to inform Healthcare Planning

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Versorgung Frühgeborener an der Grenze der Lebensfähigkeit

Teil I: Systematische Analyse der Outcomes und Ressourcennutzung zur Planung des Versorgungsaufwands für neonatologische Intensivstationen

Endbericht

Ludwig Boltzmann Institut
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Abkürzungsverzeichnis

ART .... artificial productive technology
BAPM .... British Association of Perinatal Medicine
BW .... birth weight
CI .... confidence interval
CP .... cerebral palsy
CPAP .... continuous positive airway pressure
DPR .... doctors-to-patient ratio
EP .... extreme preterm (birth)
FG .... Frühgeborene
EFG .... extrem unreife Frühgeborene
GA .... gestational age
G-BA .... Gemeinsamer Bundesausschuss (Germany)
GRADE .... Grading of Recommendations Assessment, Development and Evaluation
INSURE .... "InSuRE": Intubation, Surfactant and Rapid Extubation
LISA .... less invasive surfactant application
LOS .... length of stay
MA .... meta-analysis
NDI .... neurodevelopmental impairment
NICU .... Neonatal Intensive Care Unit
NICHD .... Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN)
NPR .... nurse-to-patient ratio
RoB .... risk of bias
RQ .... research question
SSW .... Schwangerschaftswoche
ÖSG .... Österreichischer Strukturplan Gesundheit
QoL .... quality of life
SR .... systematic review
VLBW .... very low birth weight infants

Zusammenfassung

Ziel

Ziel dieses Projektes war es, eine Übersicht der verfügbaren Evidenz zu den Outcomes extrem unreifer Frühgeborener (EFG) und zum Ressourcenbedarf für neonatologische Intensivstationen (NICUs) zu erstellen, die als Entscheidungshilfe für die Ressourcenplanung dienen kann.

Ziel: Evidenzübersicht zu den Outcomes für EFG und zum Ressourcenbedarf der NICUs

Methodik

Ein ‚Mixed Methods Design' aus mehreren Methoden wurden angewendet, um die Hauptforschungsfragen zu beantworten:

Mixed-Methods-Design zur Beantwortung der Forschungsfragen:

Zunächst wurde ein systematischer Review (SR) zu den klinischen Outcomes Überleben und Überleben ohne Beeinträchtigung in Relation zum Gestationsalter (Schwangerschaftswoche, SSW; 22 vollendete Wochen + 0 Tage bis 25 vollendete Wochen + 6 Tage) durchgeführt. Die systematische Literaturrecherche erfolgte in fünf Datenbanken (Medline via Ovid, PubMed, Embase, The Cochrane Library, CRD) und wurde auf Publikationen der letzten fünf Jahre, sowie auf sekundär Literatur beschränkt (SR, Metaanalysen, MA, HTA-Berichte).

1) SR zu Outcomes

Zur Beantwortung der Forschungsfrage nach dem Ressourcenbedarf wurde eine Literaturrecherche mit systematischer Suche in fünf Datenbanken (Medline via Ovid, PubMed, Embase, The Cochrane Library, CRD) durchgeführt. Des Weiteren wurden Daten von Statistik Austria zur Anzahl der Frühgeborenen (FG) und EFG in Österreich analysiert [2]. Zusätzlich wurden semistrukturierte Interviews mit fünf Leitern neonatologischer Intensivestationen durchgeführt, um Österreich spezifische Faktoren für die Ressourcenplanung zu identifizieren.

2) Literaturanalyse mit systematischer Suche, Datenextraktion zur Anzahl FG in Österreich Interviews

Ergebnisse

Ergebnisse der systematischen Suche zu Outcomes

Die systematische Suche ergab 233 Treffer. Davon wurden insgesamt fünf SRs für die Volltextanalyse und Qualitätsbewertung identifiziert. Auf Basis der Qualitätsbewertung mit dem AMSTAR-Tool wurden schließlich zwei SR für die qualitative Synthese der Ergebnisse ausgewählt (ein SR zu Überleben und 2 SRs zu Überleben mit neurokognitiver Einschränkung). Zusätzlich zu den SRs wurden Daten zum Überleben der EFG aus 5 Primärstudien (4 Kohorten Studien und einem österreichischen Fallregister) durch eine Handsuche identifiziert, um die Ergebnisse aus den SRs mit den Ergebnissen einzelner internationaler Studien zu vergleichen.

systematische Suche für Outcomes:
233 Treffer,
2 SR und
5 primär Studien zur qualitativen Analyse

Überleben extrem unreifer Frühgeborener

Die Ergebnisse des ausgewählten SR zum Überleben zeigten, dass 9 % der EFG der SSW 22 + 0-6, 27 % der SSW 23 + 0-6, 55 % der SSW 24 + 0-6 und 73 % der SSW 25 + 0-6 überleben, wobei die Überlebensraten als Prozentsatz der Lebendgeborenen berechnet wurden [1]. Bei der Berechnung des Überlebens als Prozent der EFG, die in NICUs transferiert wurden, zeigte sich eine Überlebensrate von 33 %, 48 % und 68 % für die SSW 22 + 0-6, 23 + 0-6 und 24+0-6 Wochen und 75 % für die SSW 25 + 0-6.

Überleben (als % der Lebendgeborenen und % der Transfers in NICUs):
22 SSW: 9 % und 33 %
23 SSW: 27 % und 48 %
24 SSW: 55 % und 68 %
25 SSW: 73 % und 75 %

Überleben extrem unreifer Frühgeborener ohne neurokognitive Beeinträchtigung

Überleben ohne schwere Beeinträchtigung: 23 SSW: 43 % 24 SSW: 47 % 25 SSW: 61 %

Die Ergebnisse der SR und MA errechneten die Chancen für das Überleben ohne schwere Beeinträchtigung mit 43 %, 47 % und 61 % bei der Geburt in den SSW 23 + 0-6, 24 + 0-6 bzw. 25 + 0-6 [1]. Für EFG der SSW 22 + 0-6, waren zu wenige Daten vorhanden, um Rückschlüsse auf die Überlebenschancen ohne Beeinträchtigung ziehen zu können.

Qualität der Evidenz

Qualität der Evidenz für die Outcomes Überleben und Überleben ohne Beeinträchtigung sehr niedrig aufgrund hoher Heterogenität und Ungenauigkeit der Studienergebnisse

Die Resultate der MAs wiesen sehr heterogene Ergebnisse in den errechneten Überlebensraten auf, insbesondere für die SSW 22 und 23. Des Weiteren waren die Fallzahlen für die Berechnungen des Überlebens in SSW 22 und 23 klein und die Konfidenzintervalle breit, was auf eine Ungenauigkeit der Ergebnisse hindeutet. Folglich wurde die Qualität der Evidenz, sprich, das Vertrauen in den Effektschätzer, als sehr niedrig eingestuft.

Im Vergleich zum Outcome *Überleben* war die Qualität der Studien und der Ergebnisse zum Outcome *Überleben mit oder ohne neurokognitiver Einschränkung* schlechter, da die Anzahl der Studien, und Fallzahl pro SSW geringer war. Die Qualität der Evidenz wurde ebenfalls als sehr niedrig eingestuft.

Trends in der Zahl der extrem Frühgeborenen in Österreich

Anzahl der FG 2016: 6675 (7,7 %), davon 350 EFG (5,2 %)

Der Trend der letzten 20 Jahre zeigt einen gegenwärtigen Rücklauf des Anteils der Frühgeburten in Relation zur Anzahl der Lebendgeborenen in Österreich, mit einer leichten Abnahme seit 2008. Im Jahr 2016 kamen insgesamt 6675 FG zur Welt, was mit 7,7 % der Lebendgeborenen einem neuen Tiefstand entspricht.

Die Zahl der EFG blieb über die letzten zehn Jahre relativ konstant, mit einem leichten Anstieg in den letzten zwei Jahren. EFG machen nur einen kleinen Anteil der FG aus, nämlich etwa 5,2 % aller FG, und 0,4 % der Lebendgeborenen. Im Jahr 2016 wurden 350 Säuglinge vor Vollendung der 28 SSW geboren (22 + 0-27+6).

Ressourcennutzung und Ressourcenbedarf

systematische Suche: 416 Treffer, 31 Publikationen für qualitative Analyse ausgewählt, wenige Publikationen auf österreichischen Kontext übertragbar

Es konnten nur wenige Publikationen zur Ressourcennutzung und zum Ressourcenbedarf für die Versorgung der EFG an NICUs identifiziert werden, die für den österreichischen Kontext relevant und übertragbar sind. Auch nach Nachfrage bei den ExpertInnen wurden kaum Publikationen für Österreich gefunden. Insgesamt ergab die systematische Suche 416 Treffer, von denen 31 zur qualitativen Analyse ausgewählt wurden. Diese Publikationen unterschieden sich allerdings sehr in den ausgewählten Forschungsfragen, Studiendesigns, und sind aufgrund ihres Kontext nur bedingt auf Österreich übertragbar.

Interviews: verbesserte Outcomes führen zur Erhöhung des Ressourcenbedarfs; Pflegefachkräftemangel spielt national wie international eine entscheidende Rolle

In den Interviews verwiesen die ExpertInnen auf einen Trend zu verbesserten klinischen Ergebnisse der EFG, nicht nur im Hinblick auf das Überleben, sondern auch im Hinblick auf Überleben ohne oder mit nur leichten Beeinträchtigungen. Dieser positive Trend ginge allerdings mit einer Eskalation des Ressourcenbedarfs einher, im Speziellen aufgrund einer Verdichtung komplexerer Fälle. Der Einsatz neuartiger, nicht-invasiver Behandlungsansätze sei ursächlich für die Verbesserung der Outcomes, erhöhe allerdings den Bedarf an ausgebildeten Pflegekräften. Kongruent mit der internationalen Fachliteratur wurde die Bereitstellung einer adäquaten Anzahl an Pflegepersonal, um auf die erhöhte Arbeitsbelastung zu reagieren, als zentrale Herausforderung für NICU-Kliniken in Österreich identifiziert. Der derzeitige Mangel an Pflegekräften führt nicht nur zu einer Verschlechterung der Überlebens- und Morbiditätsraten der EFG, sondern kann auch eine Bettensperre und Kliniktransfers zur Folge haben.

Fazit und Ausblick

Erhebung und Analyse österreichischer Daten als nächster Schritt zur Bedarfs- und/oder Kostenbestimmung

Um den Ressourcenbedarf für den österreichischen Kontext zu berechnet und zu bewerten, benötig es eine Erhebung und anschließend eine Analyse quantitativer Daten zum Ressourcennutzen der einzelnen Perinatalzentren. Österreich spezifische Daten zu den Überlebens- und Morbiditätsoutcomes der EFG, zur Krankenhausaufenthaltsdauer, und zu Unterschieden in den angewendeten Interventionen und Therapieoptionen würden Rückschlüsse auf potentielle Kosten und Ressourcenbedarf zulassen.

Executive Summary

Objective

Objective and aim

The aim of this project is to provide a decision support for resource planning of NICUs in Austria. We collected evidence on the clinical outcomes in terms of survival and survival without neurodevelopmental impairment (NDI) of extremely preterm (EP) infants, as well as evidence on the resources needed in NICUs.

Methods

mixed-methods approach:

1. SR to evaluate survival and survival without NDI

A mixed-methods approach was applied to answer the main research questions:

First, a systematic review (SR) of the clinical outcomes survival and survival without impairment in relation to gestation week (week 22+0 until 25+6) was performed. The systematic literature search was conducted in five databases (Medline via Ovid, PubMed, Embase, The Cochrane Library, CRD), limited to publications from the last five years and to secondary evidence (SR, Meta-Analysis, MA, HTA-reports).

2. Literature review, data collection on the number of EP infants, 5 interviews with heads of NICUs

Secondly, a literature review with systematic search on resource needs was conducted in five databases, and data on the number of perviable births in Austria and their characteristics was collected from Statistik Austria [2].

Additionally, five semi-structured interviews with the heads of neonatal intensive care units (NICUs) were performed, to identify Austria specific factors and inform resource planning.

Results

Identified studies for the systematic review on outcomes

systematic search in 5 databases, 2 SR selected for qualitative analysis

The systematic search yielded 233 records. A total of five SRs were selected for full-text analysis and quality assessment, and finally, based on the quality appraisal using the AMSTAR tool, two SRs were selected for the qualitative synthesis of the results.

+ data from 5 primary studies

In addition to the SRs, survival data from 5 primary studies (4 cohort studies and one Austrian registry) were identified by hand search to compare and discuss findings from the SR and MA.

Survival of EP infants

survival (as % of liveborn and % of infants transferred to NICUs):
22 GA: 9% and 33%
23 GA: 27% and 48%
24 GA: 55% and 68%
25 GA: 73% and 75%

Results from the selected SR and MA showed that the survival of infants born at the limit of viability ranged from 9% for infants born at 22+0-6 weeks, to 27% at 23+0-6 weeks, 55% at 24+0-6 weeks, and 73% for infants born at 25+0-6 weeks of GA (survival rates were calculated as percentage of liveborn infants) [1]. When calculating survival rates as percentage of infants transferred to NICUs, the survival rates were 33%, 48%, and 68% at 22+0-6, 23+0-6 and 24+0-6 weeks of GA, and 75% at 25+0-6 weeks of GA.

Survival of EP infants without neurodevelopmental impairment

survival without NDI: 43%, 47%, 61% for 23-25 weeks of GA

Results from the SR and MA showed that the chances for survival without severe impairment were estimated to be 43%, 47%, and 61% at 23, 24, and 25 weeks of GA, respectively[1]. For infants born at 22 weeks of GA, data was too limited to conclude on the chances of survival without impairment.

Quality of evidence

For survival, the results of the MAs were very heterogeneous, in particular for 22 and 23 weeks of GA, and, subsequently, the quality of evidence was rated very low. Furthermore, for survival of infants born at 22 and 23 weeks of GA, the sample sizes were too small and confidence intervals were wide, suggesting considerable impression of the results.

Quality of evidence: very low

In comparison to the data on survival, the quality of data on NDI was poorer, with a limited number of data and studies per GAs. The quality of evidence was graded to be very low for the GAs 22-25 weeks.

Trends in the amount of extremely preterm infants in Austria

The trend of the past 20 years showed a present reduction in the percentage of preterm births in relation to liveborn infants in Austria with a slight decrease since 2008. In 2016, the percentage of preterm infants was at a new low with 7.7% percent and, in absolute terms, 6675 infants born prematurely.

20 years trend: currently decrease in percentage of preterm infants

The number of EP infants remained relatively steady over the period of the last ten years with a slight increase in the last two years. EP infants account for 0.4% of all liveborn infants and 5% of preterm infants in Austria. In 2016, 350 EP infants were born.

2016: 6675 preterm infants, 350 EP infants

Resource utilization and resource needs

Publications on resource utilization and resource needs to provide care for EP infants are scare. A paucity of Austria specific literature or literature applicable to the Austrian context were available. We could only identify few publications that were relevant for the scope of this report even after having asked the interviewed experts to provide additional literature.

systematic search: 416 hits, 31 articles for qualitative synthesis

The systematic search yielded 416 hits, of which 31 were selected for qualitative analysis. However, these publications differed greatly in the selected research questions, study designs, and because of their context applicability to the Austrian context is limited.

scarcity of literature on resource needs, particularly for Austrian context

The interviewees highlighted that there is a trend towards improved outcomes of EP infants not only in terms of survival, but also in survival without or with only mild impairment. This positive trend is accompanied by an escalation of resource utilization and workload due to the complex patient-case mix. The use of novel, non-invasive treatment approaches increases the necessity of trained workforce. In line with international literature, ensuring an adequate level of nurse staff to respond to the increased workload was identified as key challenge shared amongst NICU clinics in Austria. The current shortage of nurse staff could not only lead to a deterioration of outcomes for patients, but also to closed beds and transfers from one clinic, or even one region, to another.

interviewees: improved outcomes lead to increase in resource needs

shortage of nurse staff as key challenge

Conclusion

In order to capture the resource needs for the Austrian context, data collection from perinatal centres and subsequent analysis is needed. Austrian specific data on outcomes, LOS, interventions, and also costs would allow planning of resource allocation and cost-budget as well as impact analysis.

next steps: collection and analysis of quantitative data from the Austrian context

1 Introduction

Globally, less than 1% of all pregnant women give birth extremely preterm, before the completion of 28 weeks of pregnancy [3]. In Austria, 350 infants were born extremely preterm (EP) in 2016, accounting for 0.4% of all births. [2]. Despite these relatively small number of EP births, extreme prematurity is a leading cause of infant death and short and long-term morbidity [4]. According to US data, prematurity accounts for almost 45% of children with cerebral palsy (CP), 35% with visual impairment and 25% of cognitive or hearing impairment [5].

weniger als 1 % der Geburten sind extrem unreife Frühgeborene (EFG), dennoch ist extreme Frühgeburt eine Hauptursache für frühzeitigen Tod und für Langzeitmorbidität bei Kindern

Epidemiology and management

Children born around the limit of viability are at increased risk of death both during and after delivery. They are also at risk of being born with severe medical conditions or of developing a spectrum of neurodevelopmental impairments (NDI) both leading to high morbidity [6]. The success rates of survival of EP infants have improved over time as the technological advances, pathophysiological understanding and evidence-based management push the limit of viability lower [7]. Yet, different countries and different hospitals within countries have different success rates in securing disability-free survival.

The causes of EP birth are often unknown, but the risk factors are manifold. According to Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD), the risk factors include previous experience of preterm birth, pregnancy with multiple gestations, use of assisted reproductive technology, or certain abnormalities of the woman's reproductive organs [8]. Furthermore, medical conditions during pregnancy such as various infections, high blood pressure, bleeding and many others as well as mother's ethnicity, age, or lifestyle contribute to the risk of preterm labour [9].

Gründe für Frühgeburt sind oft unbekannt, jedoch gibt es bekannte Risikofakoren, z. b. Mehrlingsgeburten und IVF-Geburten

Management options for EP birth include prevention, preparation for the delivery, as well as active and comfort care treatment options post-delivery. For the prevention of EP birth, progesterone hormone treatment and cervical cerclage (that stitches the cervix close) are the treatment options at hand [10]. When preparing for delivery, medications such as tocolytics or magnesium sulphate (that also reduces the risk of cerebral palsy) can stop or delay delivery and thus provide time for administration of corticosteroids to speed up the development of the foetus's lungs and other organs and to allow the pregnant mother to be transferred to a specialized perinatal centre [11]. At the delivery, active care options include the application of surfactant therapy, intubation, and supportive ventilation (for instance by use of continuous positive airway pressure, CPAP, LISA and INSURE approaches). Comfort care (or palliative care) treatment options aim at improving an infant's quality of life (QoL) to treat symptoms and minimize pain and suffering [12].

neben Prävention, und Geburtsvorbereitung stehen aktive wie passive Therapieoptionen zur Verfügung

Definition of preterm birth

Prematurity is defined as birth before the completion of 37 weeks of gestation (up to 36 weeks +6 days or before 37 + 0 weeks). The degrees of prematurity are typically defined by gestational age (GA) or birth weight (BW) [13].

The classification based upon GA defines preterm births as:

- Late preterm birth – GA between 34+0 weeks and 36+6 weeks
- Moderate preterm birth – GA between 32+0 weeks and 33+6 weeks

Frühgeburt ist definiert als Geburt vor der vollendeten 37 SSW, extreme Frühgeburt als Geburt vor der vollendeten 28 SSW

- Very preterm birth – GA between 28+0 weeks and 31+6 weeks
- Extremely preterm birth – GA less than 28+0 weeks

bzw. Geburt eines Kindes mit weniger als 1.000 Gramm Körpergewicht

The classification based upon BW defines degrees of prematurity as:

- Low birth weight (LBW) – BW less than 2,500g
- Very low birth weight (VLBW) – BW less than 1,500g
- Extremely low birth weight (ELBW) – BW less than 1,000g

in diesem Bericht wird Frühgeburt hauptsächlich über das Gestationsalter (GA) definiert

For the purpose of this review, we primarily used the classification according to GA, however, some studies were included that categorized preterm birth by BW. The definition based on GA is also the common measure used in guidelines (GLs) to determine the limit of viability and decide if active treatment or comfort care would be pursued [14].

Limit of viability

die Grenze der Lebensfähigkeit ist der Moment, ab dem eine realistische Überlebenschance besteht, und bestimmt die Entscheidung zu aktivem bzw. passivem Vorgehen

The limit of viability is defined as the point in foetal development at which the infant has a reasonable chance of extra-uterine survival [6]. This definition of the limit of viability is changing over time due to improvements in treatment and care and resulting improvements in outcomes, and differs in different countries [15]. However, there is a considerable consensus that with active intervention, most infants born after 25+0 weeks of GA will survive, while there is little chance for survival and survival without severe impairment for infants born below 22+0 weeks of GA [6]. The probability of survival and survival without impairment increases significantly over these few weeks, thus considered the border of viability. Determining this point with as much precision as possible is important to prevent inflicting an unnecessary burden on the infant and the family, on the one hand, yet to give sufficient chances for survival to the infant, on the other hand, is the challenge at hand. Apart from low chances for survival, chances for survival without the risk of severe and permanent disability need to be considered for decision-making at the limit of viability. Furthermore, these decisions are relevant for the sake of limiting the possible overuse as well as underuse of resources in neonatal intensive care units (NICU) [6].

Current practice in Austria

in Österreich liegt diese Grenze bei einem GA von 22-24 Wo, wobei palliatives Vorgehen bei weniger als 22 + 6 SSW, aktives Vorgehen ab 24 + 0 SSW vorgesehen ist

zwischen 23 + 0 und 23 + 6 SSW wird die Entscheidung gemeinsam mit den Eltern unter Zuziehung wichtiger Outcome-Parameter getroffen

In Austria, the limit of viability is defined as birth at 22+0 to 23+6 weeks of GA. Similarly to many other European countries such as Germany, active treatment for extremely preterm (EP) infants starts at 23+0 weeks of GA, i.e. after the completion of 23 full weeks of pregnancy, as shared decision-making process with the parents considering outcome prognosis including outcome data from the individual clinic. At 24+0 weeks of GA, pro-active care is recommended. For infants born at 22+6 weeks of GA and below, comfort care approach is pursued due to the low survival rates (0-10%) and even lower rates of survival without severe neurodevelopmental impairment (0-2%) [14]. This recommendation is based on a recently updated consensus guideline by the working group for neonatology and paediatric intensive care and the working group on ethics in paediatric and adolescent medicine of the Austrian Society for paediatric and adolescent medicine (ÖGKJ) [14]. Part two of this project on care at the threshold of viability specifically addresses differences in international guidelines on the definition and approach to care for EP infants.

The medical advances in neonatal intensive care have led to increased survival rates of EP infants in the last two decades, whereby infants born after 22+0 weeks of gestation today have a chance for survival. Still, EP infants born at the limit of viability have poor outcomes in terms of mortality and morbidity, compared to infants with a higher GA. Only few reviews exist that summarize the outcomes of infants born at the limit of viability and provide survival rates specific to GAs. Thus, it is difficult for healthcare planners to find reliable sources to estimate survival and morbidities of EP infants to be accounted for in care planning and resource allocation. Additional efforts and resources are needed to provide adequate care at the limit of viability and with the rising number of survivors, these resource needs increase as well.

die medizinischen Fortschritte der letzten Jahrzehnte haben ein Überleben EFG ermöglicht, wodurch es zu einem höheren Ressourcenaufwand kommt

Part one of this report provides an overview of the current level of evidence on outcomes in terms of survival and survival without impairment and the related resource needs of NICU clinics to inform health care planning.

dieser, sowie die derzeitigen Outcomes der EFG sollen in diesem Bericht systematisch betrachtet werden

1.1 Aim and research questions

The aim of this project is to provide a decision support for resource planning of NICUs in Austria. This project on *perinatal care at the threshold of viability* was divided into two parts, part I *Systematic Analysis of Outcomes and Resource Needs for Neonatal Intensive Care Units to inform Health Care Planning* and Part II *Decision-making at the limit of viability and professional ethics at Care Units* [16].

Ziel des Berichts und Forschungsfragen:

In this first part of the two reports, we aim to provide evidence on the clinical outcomes of extremely preterm infants as well as insights into the resources needed in NICUs for the provision of adequate care for preterm infants, to inform healthcare planning.

1. Überleben und Überleben ohne neurologische Beeinträchtigung (NDI)
2. Ressourcennutzung zur Planung des Versorgungsaufwands

The following research questions (RQ) were defined:

1. What are the *outcomes* of infants born at 22, 23, 24, and 25 weeks of gestation?
   a. in terms of survival
   b. in terms of survival without neurodevelopmental impairment (NDI)
   c. in terms of survival with NDI
2. What *resources* are needed in NICUs for the provision of adequate care for preterm infants to inform healthcare planning?
   a. in terms of health care workforce (medical doctors/nurses)
   b. in terms of hospital capacity (workforce and lengths of stay)
   c. What centre-level factors influence outcomes of extremely preterm infants?

The evidence on outcomes and mapping of resource requirements for EP infants shall provide information for the healthcare planning processes of NICUs in Austria.

It was outside the scope of this report to assess costs of resource needs and the interventions in relation to their effectiveness.

nicht:
Kosten-Nutzen -Analyse

1.2 Structure of the report

Struktur des Berichts

The report is structured as follows:

- In chapter 2, we first describe the methods applied to answer the two main research questions (RQ): the systematic review (SR) on the outcomes of EP infants in terms of survival and survival without neurological impairment to answer RQ1 and the mix-methods approach combining a literature review, and interviews to answer RQ2.
- In chapter 3, we present the findings from the SR on outcomes in terms survival and survival without impairment in relation to GA. For each outcome, the characteristics of the included literature, the results, and quality of evidence are presented. In conclusion of each subchapter, we discuss the challenges associated with interpreting outcome data on EP infants.
- In chapter 3, we address resource needs to provide care for EP infants by performing a review of literature and a qualitative analysis of interviews. We incorporate the findings of the literature and interviews in four chapters: we first describe the trends in the number of preterm birth in Austria, followed by the analysis on workforce, hospital capacity, and centre-level factors.
- In chapter 4 and chapter 5, we integrate the chapters on outcomes and on resource utilization in a summary and discussion of the results.

2 Methods

To answer RQ1, a SR of the clinical outcomes survival and survival without impairment in relation to gestation week (week 22+0 until 25+6) was performed.

RQ1:
SR zu Überleben und Überleben ohne NDI

To answer RQ2, we conducted a literature review with systematic search to gather evidence on resource needs for the provision of care for preterm infants in NICUs, and gathered data from Statistik Austria on the number of perviable births in Austria. Additionally, five semi-structured interviews with the heads of NICUs were performed, to identify Austrian specific factors and inform resource planning.

RQ2:
Literaturanalyse mit systematischer Suche, Interviews, Datenextraktion zur Anzahl FG in Österreich

2.1 Methods RQ1: Outcomes

2.1.1 PICO question

To answer research question one on the *outcome parameters of infants born at 22-25 weeks of gestation*, a SR was performed applying the PICO and inclusion criteria as listed in the table below.

PIKO-Frage

Table 2.1-1: PICO and inclusion criteria for systematic review

Description	Project Scope
Population	Extremely preterm infants (born before week 26: 22+ 0 – 25+6)
Intervention	Active treatment: Surfactant therapy, tracheal intubation, ventilatory support (CPAP, bag-mask ventilation, mechanical ventilation) parenteral nutrition, epinephrine (or other adrenaline), chest compression
Comparators	None
Outcomes	**Clinical Outcomes:** • General survival • Survival without neurodevelopmental impairment (NDI) • Survival with NDI
Setting	Neonatal intensive care units in high-income countries
Study type	Clinical Outcomes: Systematic reviews (SR), meta-analyses (MA), HTA reports
Publication period	2013-2017 (5 years)

2.1.2 Systematic literature search

The systematic literature search was conducted on the 14.06.2017 in the following databases:

- Medline via Ovid
- PubMed
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

systematische Literatursuche in 5 Datenbanken insgesamt 233 Publikationen identifiziert

After deduplication, overall 233 citations were identified. The specific search strategy employed can be found in appendix 8.3.1.

Additionally, a hand search was performed screening the reference list of relevant publications by title and abstract. The hand search identified 8 further studies, resulting in a total number of 241 search hits.

Exclusion and inclusion criteria

HTA Berichte und SRs von 2013-2017

Given the extensive body of evidence (cohort studies, SRs, and MAs), the systematic literature search was limited to SRs, MAs, and HTA assessments.

Secondary studies were retrieved in full-text version. Only the most recent reports (published in 2013-2017) were included qualitatively. SRs were assessed according to year of publication, time range, scope, and population to identify the most recent review that overlapped with the scope of the present assessment.

zusätzlich 5 Kohortenstudien

Additionally, to compare the findings of the SRs and MAs on survival outcomes and discuss challenges of comparability of international outcome data, we included 5 primary studies (4 cohort studies and one register). These cohort studies were identified by hand search, and stem from international networks of neonatology.

2.1.3 Quality assessment

AMSTAR zur Bewertung der Qualität der SR

The AMSTAR tool was used to assess the quality of SRs. Two independent researchers (KH, MS) systematically assessed the quality of evidence using the AMSTAR tool for SRs [17]. Of the five identified SRs, three had an AMSTAR rating of 8 out of 11 or above, which was considered sufficient quality. One of the reviews with an AMSTAR rating of 9 only included publications from the US context, and was published already in 2013; consequently, we did not consider it for the analysis.

Finally, the two selected studies to be included in the qualitative synthesis were i) a systemic review and HTA assessment by the Norwegian Public Health Institute (AMSTAR score of 10/11) [1], which assessed both outcomes survival and survival without NDI, and ii) a SR by Moore et al. (AMSTAR score of 8/11) [18], which assessed long-term NDI in EP infants. The AMSTAR rating for each individual study and the main characteristic of the identified reviews can be found in the appendix Table 8.1-1 and Table 8.1-2.

Zusammenfassung der Ergebnisse mit GRADE

For the assessment of the strength of evidence, the "Grading of Recommendations, Assessment, Development and Evaluation" – GRADE approach was used [19].

2.1.4 Analysis and Synthesis

Datenextraktion aus Studien

We retrieved data from the selected studies, and summarized the findings in the data-extraction-tables. No further data processing (e.g. indirect comparison) was applied. For the outcome *survival*, we compared the results of the MA with findings from 5 primary data sources (4 cohort studies and 1 register).

2.1.5 Flowchart: Outcomes

The author and the co-author screened and selected studies independently from each other; disagreements were resolved by consensus. The search yielded 233 records. A cross-reference search identified 8 additional studies. A total of five SRs were selected to assess study quality. Finally, based on the quality appraisal using the AMSTAR tool, two SR were selected for the qualitative synthesis of the results.

insgesamt 241 Publikationen identifiziert

In addition to the SRs, survival data from 5 primary studies (4 cohort studies and one Austrian registry) were identified by hand search to compare and discuss findings from the SR and MA.

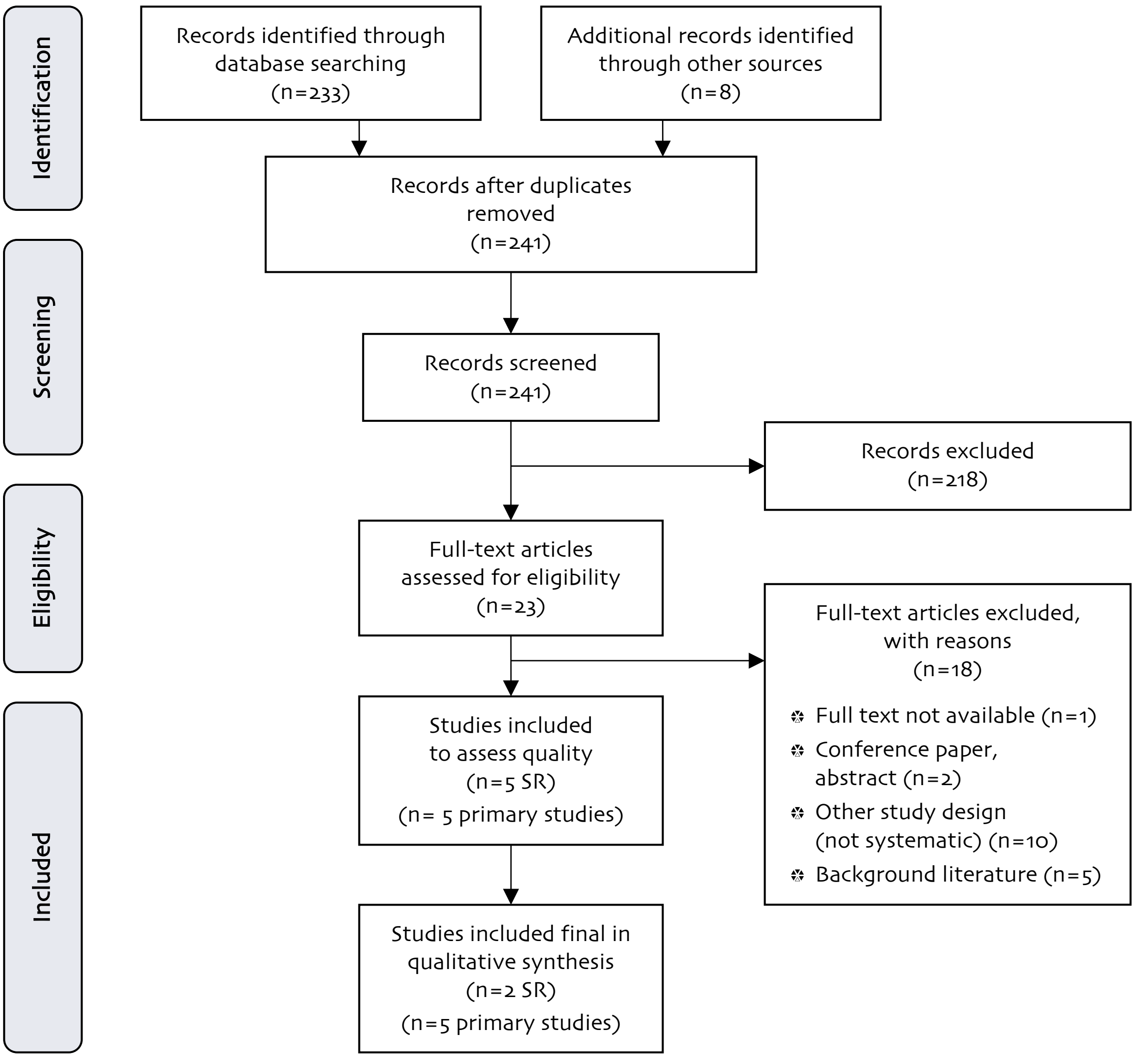

Figure 2.1-1: Flowchart for study selection outcomes (PRISMA Flow-Diagram)

2.2 Methods RQ2: Resouce needs and utilization

RQ2: systematische Suche, Literaturanalyse, Datenexkraktion zur Anzahl der FG in Österreich

A mixed-method was applied to answer RQ2 on resource needs and utilization. In a first step, a comprehensive, systematic literature search was conducted to scope the available evidence on resource needs and utilization of NICUs and perinatal centres in relation to EP infants. Additionally, data from Statistik Austria was retrieved to provide an overview of the current situation and past trends of the number of preterm infants in Austria.

Thema Ressourcennutzung sehr kontextsensibel – daher zusätzlich Interviews mit 5 österreichischen Perinatalzentren

Factors related to resource needs to inform care planning are very context specific, related to the organisational structure, epidemiology, and care pathways of a country. After screening the available literature, we subsequently decided to additionally conduct interviews with the heads of NICUs to guarantee relevance of the report to the Austrian context, provide meaningful context to international literature, and, gather the Austrian specific factors that would be pivotal for care planning of NICUs. In total, five interviews with the heads of five perinatal care centres[1] in Austria were conducted to get an overview of the resource needs and efforts for EP infants in the Austrian context.

The results of both the literature review and the interviews were analysed separately and subsequently integrated into the results part of this chapter.

Definition of resource needs and resource utilization

Ressourcenaufwand durch spezifische Kategorien definiert um systematische Suche zu ermöglichen: Personal und Kapazität der NICUs

In an initial scoping exercise, we delineated the concept of resources for NICUs to broad categories with specific endpoints that would enable a systematic search. The choice of the two main concepts *workforce* and *hospital capacity* with their respective endpoints were discussed with the heads of NICUs to ensure relevance and applicability to the Austrian context. Figure 2.2-1 depicts the model that was applied to define the search terms.

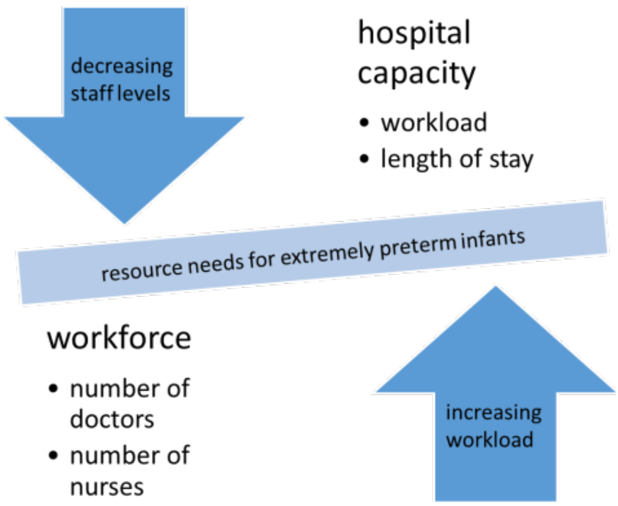

Figure 2.2-1: Model to delineate the concept of resource needs

[1] Perinatal care centres in Austria represent the highest level of specialization for neonatal care, and correspond to level 1 perinatal care centres in Germany; and level 3 tertiary care centres in the UK

2.2.1 Literature review

Systematic literature search

To identify as much relevant literature as possible, a systematic search was applied. Additionally, a comprehensive hand search based on references lists from relevant publications was conducted.

systematische Suche in 5 Datenbanken

The systematic literature search was conducted on the 16.06.2017
in the following databases:

- Medline via Ovid
- PubMed
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

Additionally, a hand search was performed by screening reference lists of relevant publications, whereby 28 additional articles were identified. The specific search strategy employed can be found in appendix 8.3.2.

zusätzlich Handsuche

Selected Endpoints

In order to select relevant literature and delineate the concept of resource needs and resource utilization, the following endpoints were defined for the systematic search:

ausgewählte Endpunkte:

- Research on Health Personnel and workforce in NICUs
  - Research on workforce on NICUs
  - Nurse-to-patient ratio (NPR)
  - Doctors-to-patient ratio (DPR)
- Research on hospital capacity:
  - Length of stay (LOS)
  - Workload

Gesundheitspersonal:
- Pflegequote (NPR)
- ÄrztInnenquote (DPR)

Zentrumskapazität:
Aufenthaltsdauer
Arbeitsaufwand

Inclusion and exclusion criteria

We limited our search to the last ten years (2008-2017), to articles in English or German, and to articles from high-income countries. The systematic search was not limited to a specific study design.

While we did not explicitly state it as inclusion or exclusion criterion, endpoints in relation to gestation week were of particular interest in order to answer the research questions.

Einschlusskriterien:
Publikationszeitraum: 2008-2017
englische oder deutsche Publikationen

Since this report was planned to be solely literature driven, we did not evaluate costs of care in the Austrian context. One reason for this literature driven approach is the lack of accessible and available data needed for a budget- and cost-analysis. In this regard, we also refrained from including literature on cost from other countries, due to lacking applicability and limited comparability with the Austrian context. Since we did not evaluate the effectiveness of a certain intervention, cost-effectiveness analyses on different treatment methods were excluded as well.

keine Kostenanalyse aufgrund fehlender österreichischer Daten

Flowchart: Resource needs

insgesamt 416 Publikationen identifiziert davon 31 ausgewählt für qualitative Analyse

In total, we identified 388 hits in the systematic search and 28 by hand searching. The references were screened by two independent researchers and in case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 2.2-2.

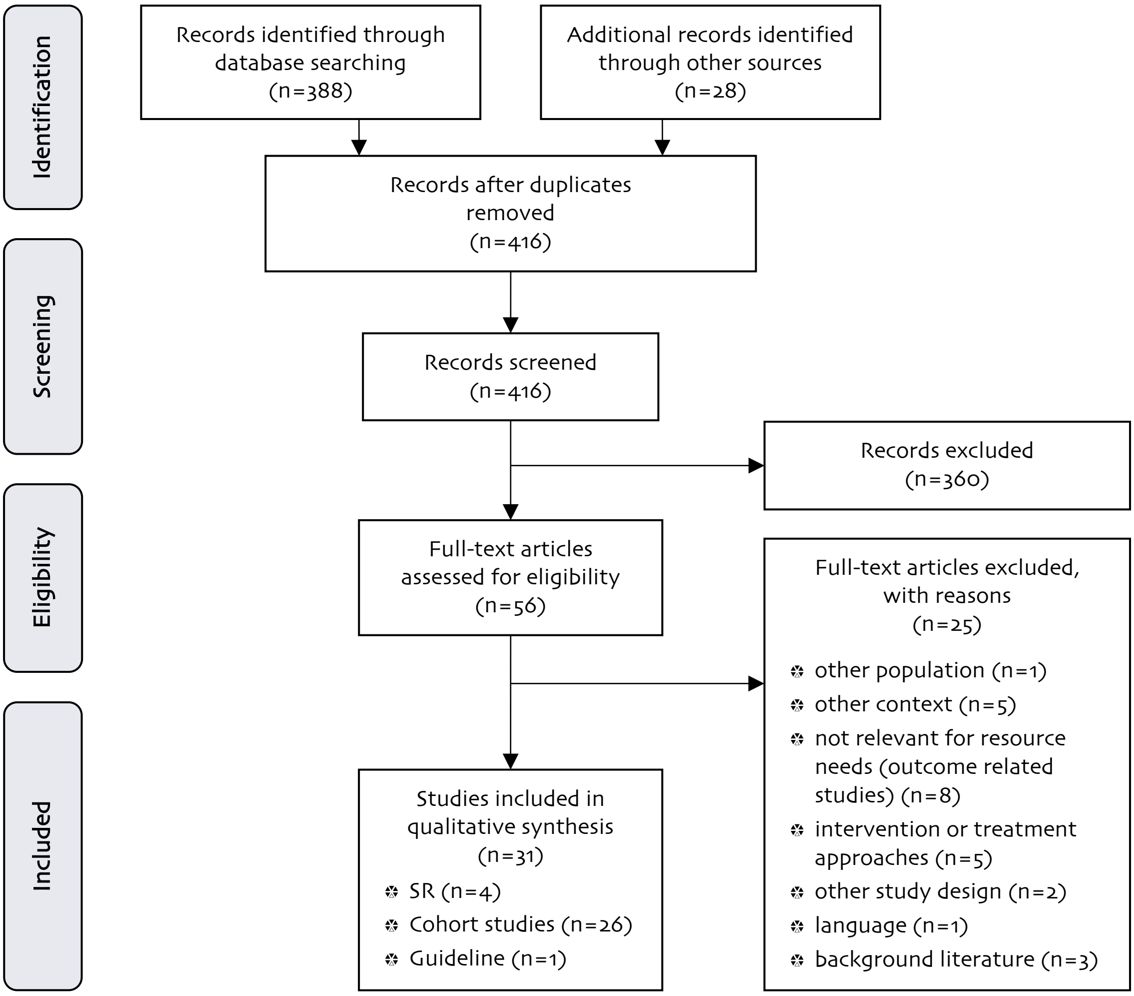

Figure 2.2-2: Flowchart of study selection resource needs (PRISMA Flow Diagram)

2.2.2 Data on periviable births in Austria

Daten für die FG Anzahl in Österreich und deren Charakteristika von Statistik Austria

We retrieved data on the number of preterm infants in Austria from Statistik Austria [2]. This data is available on the website from Statistik Austria 'Statistik der natürlichen Bevölkerungsbewegung', and was issued on 13/07/2017, and accessed in October 2017. Statistik Austria provides data on the number of preterm infants as percentage of liveborn infants in Austria. The data from the years 1995-2010 has been revised by Statistik Austria regarding the lengths of pregnancy, due to reporting differences in the earlier years.

2.2.3 Interviews

Five semi-structured interviews were conducted with the heads of NICUs in Austria (Table 2.2-1). In total, we interviewed five of seven heads of perinatal centres in Austria. Additionally, one clinical ethics specialist from the University of Vienna was interviewed, findings of this interview will be presented in part II of the report.

Interviews mit KlinikleiterInnen aus 5 Perinatalzentren

Interviews

Interviews were conducted in person or via phone call. All interviews were audio-recorded and transcribed verbatim afterwards. Verbal consent was given by all interview participants prior to recording, audio proof of verbal consent has been collected.

Interviews wurden aufgenommen und verbatim transkripiert

An interview topic list was developed to guide the interview in a semi-structured way. The research questions served as orientation to design the interview guide. The interview topic list can be found in the appendix.

2 WissenschaftlerInnen führten, kodierten und analysierten die Interviews

The interview duration ranged from 30 to 60 minutes; one single interview lasted one hour and 40 minutes. Two researchers conducted and coded the interviews. Interviews were held in English, in some cases, clarifications were phrased in German.

Interviewsprache war Englisch

Prior to data analysis, interview summaries were sent to the interviewees to confirm the results. If necessary, changes were made in the transcripts, and summaries. Moreover, the final quotations and analysis were confirmed with interviewees.

Interviewzitate und Paraphrasierungen wurden TeilnehmerInnen zur Bestätigung gesendet

Table 2.2-1: Overview of interview participants

Perinatal center	Name	Function
Medical University Graz	Univ.-Prof. Dr. Urlesberger	Head of the department for neonatology
Medical University Innsbruck	Univ.-Prof. Dr. Kiechl-Kohlendorfer, MSc	Head of the department for neonatology, deputy director department pediatric care
Kepler University clinic, Linz	Prim. Dr. Wiesinger-Eidenberger	Head of the department for neonatology
University clinic Salzburg	Priv-Doz. Dr. Wald	Head of the department for neonatology
Medical University Vienna/ AKH Wien	Univ.-Prof. Dr. Berger, MBA	Head of the Department of Neonatology, Pediatric Intensive Care and Neuropediatrics, Deputy Director of the Department of Pediatrics and Adolescent Medicine

Data analysis

To analyse the transcripts a combination of open coding and structured thematic analysis was applied. This analysis was performed starting with fragmentation and open-coding of each transcript. Thereby, every fragment received a code, such as a word or short sentence to identify themes. The main codes and themes were organised in a code-tree, which can be found in the appendix Table 8.2-1. In addition to open-coding, the thematic themes from the interview topic list served as structural guideline to analyse the interviews. Subsequently, the results of all interviews were edited and common themes and codes integrated. Data analysis was performed using the qualitative data analysis software Atlas.ti (Version 8).

Analyse der Interviews nach Kodierungsschema: offen und strukturierte Inhaltsanalyse

2.2.4 Quality assurance

interner und externer Review …

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- Technical correctness: Is the report technically correct (evidence and information used)?
- Does the report consider the latest findings in the research area?
- Adequacy and transparency of method: Is the method chosen adequate for addressing the research question and are the methods applied in a transparent manner?
- Logical structure and consistency of the report: Is the structure of the report consistent and comprehensible?
- Formal features: Does the report fulfil formal criteria of scientific writing (e.g. correct citations)?

… als Methode der Qualitätssicherung

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

3 Outcomes of extremely preterm infants

3.1 Survival of extremely preterm infants

In this section, we first describe the findings from the systematic search and the results from the identified MA on survival of EP infants at 22+0 to 25+6 weeks of GA. We evaluate the quality of evidence of the MA, and subsequently compare the results from the MA with findings from international cohort studies. Finally, we conclude by outlining the challenges with interpreting outcome data.

Gliederung des Kapitels

3.1.1 Characteristics of included secondary studies

We identified one SR that met the inclusion criteria. This review applied a similar PICO question to analyse the selected endpoints survival and survival without impairment of EP infants and had a high rating of 10 out of 11 scoring points when assessing the quality of evidence with AMSTAR. The review was published in 2017 by the Norwegian Institute of Public Health [1]. The objective was to evaluate the prognosis for EP infants that received active life-saving treatment in terms of survival and survival with morbidities. The SR was published in Norwegian language, and was thus translated into English and German by a translator.

1 SR zu Überlebensoutcomes identifiziert und inkludiert

Table 3.1-1 depicts the characteristics of the study and exclusion and inclusion criteria. The primary outcome was survival; the secondary outcomes were survival with co-morbidities such as cerebral palsy (CP), autism, impaired vision, lung problems, and school performance.

primärer Endpunkt des SR: Überleben sekundäre Endpunkte: Überleben mit Komorbiditäten

The search period of the SR comprised 15 years (January 2000 – June 2015). The final search yield 5420 hits, whereby 506 articles were screened for full-text analysis and a final 52 studies were included in the SR. The 52 included studies were cohort studies and the study sample consisted of a total of 53,013 infants born before the completion of 28 weeks of GA (27+6), and after 22+0 weeks of GA. The cohort studies were published in the period from 2004 to 2015, and the infants were born in the period from 1996 to 2011. The studies originated from 18 high-income countries: Austria, Australia, Belgium, Canada, England, Finland, France, Japan, Netherlands, Norway, Portugal, Singapore, Spain, Switzerland, Sweden, Taiwan, Germany, and the USA.

SR enthielt 52 Studien mit insgesamt 53.013 Frühgeborenen

Of the 52 studies, 47 studies estimated survival of infants born in weeks 22+0-27+6 and 22 studies reported data on morbidity of extremely premature infants, of which 10 studies reported on neurological impairment.

Meta-Analysis

die Auswertung der MA erfolge in „R"

The MA used a random effects model and were conducted in 'R' [20]. The weight of different studies was determined by the size of the studies.

MA für zwei Gruppen:
- Überleben als Prozentsatz aller Lebendgeborenen
- Überleben als Prozentsatz der FG, die in NICUs transferiert wurden

Since the included studies were using different denominators (survival rates measured as percentage of liveborn infants, or as percentage of infants transferred to a NICU) Myrhaug et al. [1] calculated two sets of MAs:

1. Meta-analysis for the survival of preterm infants who were admitted to NICU, and
2. Meta-analysis for the survival of liveborn infants.

The MA included 23 studies that all had low risk of systematic bias. The studies considered in the MS are marked with an asterisk in Table 3.1-1.

Table 3.1-1: Main characteristics of the included systematic review on survival outcomes

Author, year	Study type	Aim of the study	Intervention/ Exposure vs Comparison	Main endpoints	Inclusion criteria	Exclusion criteria	Included studies (N=52)*	Databases searched	Search period	AMSTAR
Myrhaug et al. 2017 [1]	SR, MA	To evaluate the prognosis for extremely premature infants who have undergone acute life-saving treatment for a) survival and b) morbidity from discharge	• Exposure: • being born extremely premature • Comparison: none	• Primary outcomes: survival at discharge, at one to ten years. • Secondary outcomes: Cerebral Palsy, autism, impaired vision, lung problems, school performance, and/or another health-related outcome from discharge to home for cohorts and with ≥5 yrs follow-up time for RCTs	• Population: EP infants born with GA 22-27 weeks. • Context: high-income countries, children born from 1998 until 2015 • Study-design (in order of priority): • 1. Systematic overviews of cohort studies; • 2. Systematic overviews of RCTs, • 3. Cohort studies (as of 2000) • Language: English, German, French, Norwegian, Swedish and Danish	• Studies that were not published in full text, • studies that reported only birth weight, • studies published before 2000, • studies from low and middle-income countries, • studies that only examined prognostic factors and prognostic factor-models, • RCTs identified via systematic overviews with less than 5 years follow-up time on secondary outcomes	Abdel-Latif, 2013; Agarwal, 2013; Ancel, 2015*; Berger, 2012*; Binet, 2012; Bode, 2009; Bode-Livinec, 2008*; Bolisetty, 2015*; Boussicalt, 2012*; Costeloe, 2012*; D'Amore, 2011; DeGroote, 2007; deWaal, 2012*; Doyle, 2010; Fellman, 2009; Fischer, 2009*; Herbert-Jonat, 2006*; Hintz, 2011; Holmstrøm, 2014; Ishii, 2013; Itabashi, 2009*; Jacobsen, 2009; Klebermass-Schrehof, 2013; Kutz, 2009; Kyser, 2012; Landmann, 2008*; Leversen, 2010; 2011; Malloy,2015; Markestad, 2005*; Michikata, 2010; Moore, 2012; Morgillo, 2014; Munck, 2010; Nguyen, 2012; Poon, 2013; Rieger-Fackeldey, 2005; Rocha, 2011; Rodrigo, 2015; Schlapbach, 2012; Seaton, 2013; Serenius, 2013*; Sommer, 2007; Stichtenoth, 2012*; Stoll, 2015*; Su,2015; Sugiura, 2011; Vanhaesebrouck, 2004*; Veit-Sauca, 2008; Weber, 2005*; Wong, 2014; Zayek, 2011*, Zetlin, 2010	MEDLINE, PubMed, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and CINAHL	2000-June 2015	10

Abbreviations: AMSTAR = A Measurement Tool to Assess Systematic Reviews, MA = meta-analysis, RCT = randomized controlled trial, SR = systematic review, yrs. = years; studies with asterisk were included in the MA

3.1.2 Findings: Survival of infants born at 22- 26 week of GA

22 weeks (22+0 – 22+6)

Überlebensrate von FG 22 SSW 9 % (% Lebendgeborene) 33 % (% in NICU transferiert)

The MAs showed that survival rates for infants born at 22 weeks of GA was 9% as percentage of liveborn infants (n=3,429; 95% CI: 3-22) and 33% as percentage of infants transferred to a NICU (n= 285; 95% CI: 27-40).

There was a large variation in results between the two sets of MAs on liveborn infants and on transferred infants. Furthermore, the heterogeneity in between the results was very high (I^2=58%).

NICU-Transferrate: 12,5 %-82 %

Only few studies reported the proportion of infants that were transferred to the NICU. Thereby, a large difference in the number of transferals was noted, ranging from 12.5% of transferred infants in one study to 82% in another study.

hohe Variabilität der Resultate

In order to find explanations for the large variance in the results between studies, an additional subgroup analysis was performed for both denominators and grouped by different follow-up times. The authors did not find any subgroup effects since this second analysis also showed a very high variation in the results (I^2>93%).

23 weeks (23+0 – 23+6)

Überlebensrate von FG 23 SSW: 27 % (% Lebendgeborene) 48 % (% in NICU)

The survival rate for infants born at 23 weeks of GA was 27% as percentage of liveborn infants (n=5,396; 95% CI: 12-51) and 48% as percentage of infants transferred to a NICU (n=1,052; 95% CI: 31-66).

starke Schwankungsbreite in Fallzahl: 13-282 FG NICU-Transferrate: 64 %-93 %

The analysis showed a large variation in the reported survival rates of the studies (I^2>94%). For example, in the MA of liveborn infants transferred to NICUs, survival ranged from 8% in a Belgium study [21] to 68% in a study from the US [22]. There was also a high variation in sample sizes, ranging from a total of 13 infants to 282 infants. The proportion of liveborn infants transferred to the intensive care unit were higher than for 22 weeks GA, and ranged from 64% to 93%.

24 weeks (24+0 – 24+6)

Überlebensrate von FG 24 SSW: 55 % (% Lebendgeborene) 68 % (% in NICU)

The survival rate for infants born at 24 weeks of GA was 55% as percentage of liveborn infants (n=1,635; 95% CI: 39 -70) and 68% as percentage of infants transferred to a NICU (n=1,255; 95% CI: 51-81).

Starke Schwankungsbreite in der Fallzahl: 13-423 FG NICU-Transferrate: >80 %

Overall, there was a large variation in the reported survival rates between the different studies (I^2>90%). For infants transferred to the NICUs, survival varied from 23% in a study from the Netherlands [24] to 96% in a study in Germany [25]. Again, the studies also varied in sample sizes, ranging from 13 to 423 infants. Of the studies that reported data on the proportion of transferals, the proportion of liveborn infants transferred to the NICU was more than 80%.

25 weeks (25+0 – 25+6)

Überlebensrate von FG 25 SSW: 73 % (% Lebendgeborene) 78 % (% in NICU) keine Daten zur Transferrate

The survival rate for infants born at 25 weeks of GA was 73% as percentage of liveborn infants (n=6,440; 95% CI: 65-81), and, similarly, 78% as percentage of infants transferred to the NICU (n= 1,859; 95% CI: 69-85).

No explicit information on transfer rates and study variance was available for 25 weeks of GA in Myrhaug et. al.[1].

Survival at ≥ 26 weeks

The survival rate among liveborn infants at 26 weeks of GA was 84% (n= 1,370; 95% CI: 78-89), survival rate as percentage of infants transferred to the NICU was similarly 85% (n= 7692; 95% CI: 73-92) [1].

Überlebensrate von FG 26-27 SSW: 84 %
in NICU: 85 %

The survival rate among infants born at 26 to 27 weeks of GA was significantly higher than among infants born at 22 to 25 weeks of GA. Furthermore, the prognosis estimates in these analyses were less heterogeneous. Statistically, the heterogeneity also remained high in these MAs, but the balance charts showed that the variation is less pronounced in the survival analysis for births at 26 and 27 weeks of GA [1].

Schwankungen geringer als bei 22-25 Wochen alten Säuglingen

Figure 3.1-1 summarizes the results from the two sets of MAs on the survival rates as percentage of liveborn infants and liveborn infants transferred to NICUs. The difference between the two reported denominators decreases with increasing GA, whereby at 26 weeks of GA the calculation of survival rates showed almost identical outcomes with rates of 84% and 85%, respectively. This shows that the choice of denominator has high impact on the reported outcome rates: at 22 weeks of GA the reported survival rates could vary as much as 24%, where either 9% or 33% of infants survive.

je höher das GA, desto geringer die Unterschiede der Berechnung des Überlebens als % der Lebendgeborenen oder % der NICU-Transfers

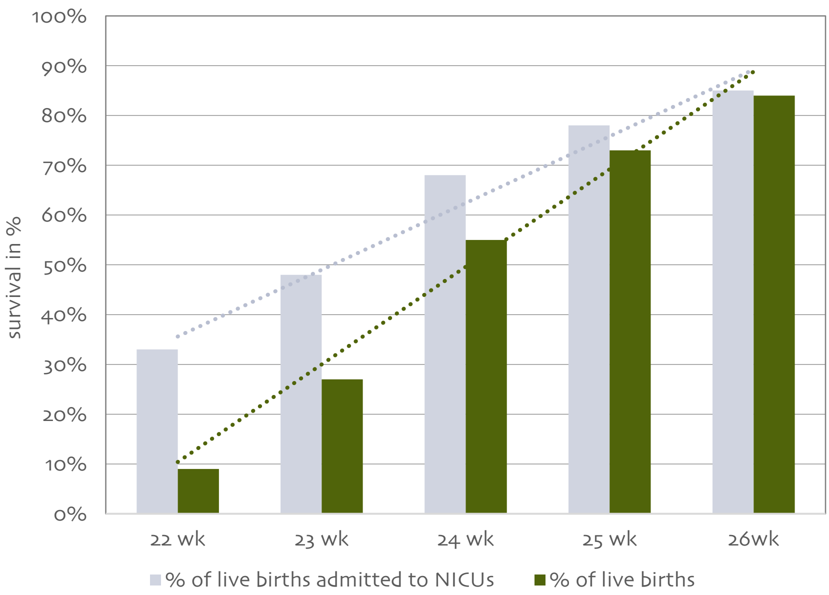

Figure 3.1-1: Survival of extremely preterm infants, adapted from data by Myrhaug et al. [1]

3.1.3 Summary of findings and quality of evidence

Risk of bias assessment

die Bewertung des Risikos für Bias erfolgte über anwendungsspezifische Checkliste

The RoB assessment of the SR by Myrhaug et al. was performed with a customized checklist assessing representativeness of study participants, reliable measurement of outcome and exposure (e.g. the method of determination of GA), sufficient follow-up time to detect positive and negative outcomes, dropout analysis, and blinding of assessors [1].

26 Studien mit niedrigem Bias-Risiko eingestuft

Out of the 47 included studies that assessed survival, 26 were considered to have low RoB by the authors of the SR.

GRADE

GRADE wurde zur Bewertung der Qualität der Evidenz eingesetzt

Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to evaluate the quality of evidence for the outcomes survival at birth with a GA of 22-25 weeks.

We re-evaluated the quality of evidence and confidence in the effect estimates of the MAs and added grading for survival estimates at 25 weeks of GA, since Myrhaug et al.[1] only assessed the quality of evidence for weeks 22, 23 and 24. We derived at different conclusions when grading the quality the evidence for survival than the authors of the MAs. This was due to the fact that the included studies were cohort studies, and consequently provide 'low quality of evidence'. While Myrhaug et al. started grading at 'high quality of evidence', we concluded that due to the observational study design a lower starting point would be more accurate [19]. We did not re-evaluate RoB of the individual studies.

Qualität der Evidenz wurde als sehr gering eingestuft

aufgrund hoher Heterogenität und Inkonsistenz der Resultate

We concluded that the quality of the evidence for survival was very low due to the high heterogeneity in between studies and the imprecision of the studies:

- There are considerable uncertainties on the estimates for survival of preterm infants, especially for weeks 22 and 23 GA, as depicted by the large confidence intervals in Table 3.2-3. The MAs show a trend of steadily increasing survival rates with increasing GA, and shrinking differences in the results between the two different denominators that were used to report survival rates (as percentage of liveborn or as percentage of infants transferred to the NICU).
- The quality of evidence was graded to be very low, due to the large variety of observed survival across the included studies. Only studies with low RoB were included in the MAs by Myrhaug et al., however, the results in between the studies showed high heterogeneity with consistently high I^2 of above 90%, and non-overlapping confidence intervals of several studies. The subgroup analyses of studies grouped by different follow-up times (survival until discharge, one- or two-year survival) could not explain the variation in the results.

Table 3.1-2: GRADE summary of findings table for survival of EP infants at 22-25 weeks of GA

Gestational Age	Denominator	Number studies	Number of participants	Survival % (95% CI)	Quality
22+0-22+6 weeks GA	% of infants transferred to NICU	7	98/285	33% (CI: 27-40)	⊕◯◯◯ VERY LOW[2]
	% of live births	15	424/3429	9% (CI: 3-22)	⊕◯◯◯ VERY LOW[1, 2]
23+0 – 23+6 weeks GA	% of infants transferred to NICU	9	516/1052	48% (CI: 31-66)	⊕◯◯◯ VERY LOW[1]
	% of live births	17	1635/5396	27% (CI: 12-51)	⊕◯◯◯ VERY LOW[1]
24+0 – 24+6 weeks GA	% of infants transferred to NICU	11	1255/1923	68% (CI: 51-81)	⊕◯◯◯ VERY LOW[1]
	% of live births	18	1635/5396	55% (39-70)	⊕◯◯◯ VERY LOW[1]
25+0 – 25+6 weeks GA	% of infants transferred to NICU	11	1859/2414	78% (69-85)	⊕◯◯◯ VERY LOW[1]
	% of live births	19	6440/8839	73% (65-81)	⊕◯◯◯ VERY LOW[1]

Notes: only studies with low RoB were included in the meta-analysis; the study design was observational studies (cohort studies); adapted from meta-analysis by Myrhaug et al., 2017 [1]

[1] *(-1) inconsistency: high degree of heterogeneity among studies ($I^2 > 90\%$)*

[2] *(-1) imprecision: broad Cis, small sample sizes*

Comparison of international data on survival of EP infants

Cohort studies from various countries provided GA-specific survival data for EP infants, for example, the US, France, Japan, Taiwan, the United Kingdom, Sweden, and Singapore. The results from these cohort studies were included in the MA by Myrhaug et al.[1]. One finding of this MA is the high degree of variance in the reported outcomes in between studies, particularly for infants born at 22 or 23 weeks of GA. Differences in management approaches, in the provision of care at the limit of viability and in quality of care were suggested as underlying reasons for the considerable variance between countries [26]. Furthermore, international comparisons are limited by differences in definitions, data sources, and use of denominators [4].

hohe Varianz der Ergebnisse der internationalen Kohortenstudien, besonders bei SSW 22-23 (22+0-23+6) Wochen

In order to highlight the variations in the survival outcomes of EP infants in between different studies, the results from the MA by Myrhaug et al. are compared with several large cohort studies in Figure 3.1-2. We only considered studies that reported survival as percentage of liveborn infants, to align the denominators used. Outcome data for Austria was retrieved from the recent consensus guideline on care at the limit of viability and is based on data from the early-born outcome register [14]. Table 3.1-3 presents the characteristics of the cohort studies used for the comparison, in terms of context, birth years and sample size.

Vergleich der Ergebnisse der MA und einzelner Kohortenstudien um Unterschiede der Ergebnisse aufzuzeigen

The graph in Figure 3.1-2 depicts the variation in survival rates between different cohorts and studies. The variation is highest at 23 weeks of GA, but remains high at 25 weeks of GA, with differences in survival rates ranging from 60% in the Epipage cohort [27] to above 80% in the Express cohort [28].

Unterschiede in Ergebnissen für GA 23 am höchsten

Österreich: Überlebensrate von FG der 23 SSW: 45 %; FG der 24 SSW 70 %

Frankreich: niedrigste Überlebensraten

The cohort in Sweden, followed by the one in Austria achieved the highest survival rates of infants born at 23 and 24 weeks of GA with over 50% and 45% of infants at 23 weeks surviving, and 70% of infants of at 24 weeks surviving, respectively. The Epipage study in France showed the lowest survival for these infants, with hardly any survivors at 23 weeks and only 30% at 24 weeks of GA. The outcomes of the EpiCure study [29] and the results from the NICHD network [30] showed comparable results to the calculated MAs, although the NICHD network consistently achieved better results, while the EpiCure study showed lower outcomes at 24 and 25 weeks of GA.

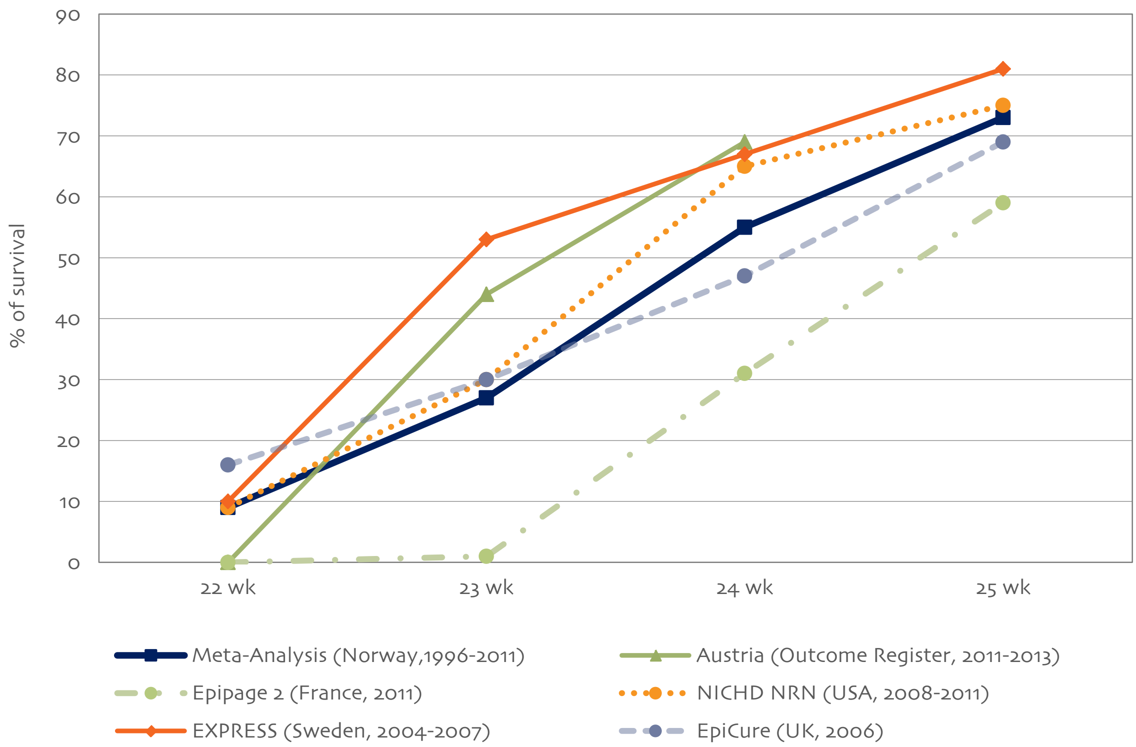

Figure 3.1-2: Survival rate of extremely preterm infants (22+0-25+6) as percentage of live births
*Notes: *In Austria and France, resuscitation of extremely preterm infants starts at 23+0 weeks GA*

Table 3.1-3: Characteristics of selected studies reporting GA specific survival rates

Study	Country & Region	Study years	Sample Size	Nominator	Denominator
Norway; MA [1]	International, results from 18 countries	1995-2011	MA of 27 studies	Mixed nominator*	Live births
Austria, outcome register for preterm birth	Data from all NICU clinics in Austria (voluntary provision of data)	2011-2013	Not publicly available information	Not publicly available information	Live births
Epipage 2 [27]	26 regions in France	2011	1911	Survival to discharge	Live births
NICHD NRN [30]	26 NNR sites, USA	2008-2011	7124	Survival to discharge	Live births
Express[28]	Sweden	2004-2007	707	Survival to one year	Live births
EPICure [29]	UK, Ireland	2006	2034	Survival to discharge	Live births

Notes: Study and data characteristics to compare international cohorts with outcomes of the meta-analysis. Results from all studies, but Austria are included in the meta-analysis by Myrhaug et al.2017,
**sub-analysis was calculated for survival to discharge and survival up to one year*

3.1.4 Challenges interpreting outcome data

Recent data from several countries report advances in survival rates, even for very preterm infants. These data represent a major part of developed countries, ranging from large parts of Europe, to Japan, Taiwan, and tertiary level networks in academic centres of the US. For instance, the US-based Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network estimated that 74% of EP infants today survive initial hospitalization [4]. According to the NICHD, survival is substantially improving with each gestational week, ranging from around 5% at 22 weeks, to 60% at 24 weeks, and above 90% if born after 27 weeks [4].

Überlebensraten der EFG steigend: laut NICHD überleben 74 % initialen Krankenhausaufenthalt

die Überlebens-Wahrscheinlichkeit steigt mit GA: 5 % bei 22 Wochen, 60 % bei 24 Wochen, 90 % bei >27 Wochen

These international data on survival of EP infants provide an important starting point to understand variations in outcomes and to foster discussions on management and best-practise for EP infants. However, despite the increasing data on mortality of preterm infants, interpreting these data must be done cautiously due to different data sources, considerable variability in clinical practice, management at the limits of viability, and attitudes of physicians on care at the limit of viability. The latter two are discussed in part II of the report [16].

Auswertung und Interpretation der Daten mit Vorsicht

The following aspects should be considered when comparing outcome data:

Accuracy of gestational age and other factors

Indicated above, GA is the most important factor determining viability of preterm infants. However, to determine and ascertain the accurate GA is challenging. GA estimations based on very early ultrasound deliver the most exact estimates, yet with a possible imprecision of a few days [6]. If estimates are based on the last menstrual period and/or second-trimester ultrasound, there is a possible range of imprecision of up to two weeks [31]. Furthermore, cohort studies often fail to report the method of determining GA, which might introduce a bias when comparing study outcomes [1]. Survival estimates based on GA are consequently not sufficient to predict an accurate prognosis of a preterm child.

GA wichtigster Faktor zur Einschätzung der Lebensfähigkeit allerdings: Feststellung des korrekten GA je nach Methode ungenau

Other factors affecting survival rates in EP infants are birth weight (BW), gender, plurality, and the use of antenatal corticosteroid therapy [32-34]. Similarly as to GA, also other data, such as estimation of weight before birth rely on ultrasound evidence, which may vary by as much as 15%. Small changes in weight, may have significant impact on the estimated outcome data [32].

A large cohort study by the NICHD on 4,446 infants born at 22 to 25 weeks of GA showed that the following factors are associated with improved survival and outcome: 100g increments in birth weight at a given GA; female sex, use of antenatal glucocorticoids, and singleton births. Based on these results, a web-based tool was developed to provide meaningful estimates of survival [35][2].

weitere Faktoren müssen für Überlebensprognose beachtet werden:
- Geschlecht
- Fetale Lungenreifung (antenatale Glucokortikoide)
- Einlings- oder Mehrlingsgeburten

[2] The tool is free of charge and its validity has been validated by several studies. It is not intended as sole indicator for decision-making, but can support the counselling of parents.

Differences in data sources and denominators

unterschiedliche Datenquellen und Denominatoren limitieren Studienvergleiche

Another factor that limits the comparability of outcome data are the differences in the data sources and denominators applied. There is no consensus which denominator is best to utilize when reporting outcome data [36, 37]. An infant born at 23 weeks of gestation might have one in three outcomes:

- it could be stillborn,
- it could be born alive, but not survive beyond the delivery room,
- it could be born, resuscitated and transferred to the NICU.

Überleben anhand unterschiedlicher Denominatoren gemessen:
- Anteil Neugeborenen (inklusive Totgeburten)
- Anteil der Lebendgeborenen
- Anteil der NICU-Transfers

Outcome data could then be reported

- as the number of infant survivors as percentage of all infants born within 23 weeks of GA (whether liveborn or stillborn),
- or as percentage of all liveborn infants within 23 weeks of GA (whether they survived transport to the NICU or not)
- or as percentage of infants transferred to the NICU within 23 weeks of GA [36].

führt zu signifikanten Unterschieden in den berechneten Überlebensraten

The use of different denominators leads to significant differences in the survival estimates. A SR by Guillen et al. revealed that across 111 cohort studies on survival of EP infants survival rates to hospital discharge ranged from 26.5% to 87.8%, whereby survival varied significantly between different denominators used [37]. Calculating survival

- with percentage of *all births* as the denominator, the results were 45.0%;
- using the denominator *live births,* it was 60.7%; and
- using *NICU admissions,* it was 71.6%.

Studien berichten Überleben oft nur anhand eines Denominators

The reported denominators vary greatly in between studies, whereby most studies report data on one denominator only. Out of 111 publications, only 51 specified the denominator: 6 studies used percentage of all births, 25 used live births, and 20 used NICU admissions. Furthermore, data sources vary, whereby cohort study inconsistently report baseline characteristics of patients.

Impact of variation in active treatment on survival

Unterschiede im Umgang mit der Versorgung an der Grenze der Lebensfähigkeit hat entscheidenden Einfluss auf das prognostizierte Überleben

große Unterschiede in Interventionsraten zwischen einzelnen Zentren

Variation in active treatment of EP infants has a major impact on the predicted survival, in particular for infants at the limit of viability of 22 and 23 weeks of GA. The differences in the initial management between countries and within countries account for a significant part of the variations in outcome data of different studies [4]. A multicentre study revealed that among 24 academic centres in the US, 78% of the variation in survival of infants born before 26 weeks of GA was associated with differences in the use of life-saving interventions (e.g. intubation, ventilation) [38]. The variation in mean rates of active treatment for infants at 22 and 23 weeks of GA ranged from 0% to 100% and 25% to 100% respectively in different academic hospitals. When infants that did not receive active treatment are included in population estimates of survival, a bias is created. This might lead to a misinterpretation of results since the possible outcomes if resuscitation was tried are not considered. For instance, while the reported outcome for infants of at 22 weeks of GA was 5% in the described study, this estimate changes to 23% when survival is calculated for only those infants that received active treatment [38]. While it is a more complex decision whether to provide treatment for infants at the limit of viability, these findings make it evident that understanding these data is vital for adequate counselling of parents [4]. This issue is further discussed in part II of the project [16].

3.2 Neurodevelopmental outcomes after extreme prematurity

Neurodevelopmental impairment (NDI) is the crucial long-term complication associated with extreme prematurity.

Definition Beeinträchtigung der neuro-kognitiven Entwicklung (NDI)

The term neurodevelopmental outcome refers to neurologic, cognitive, and/or sensory outcomes. NDI is defined as having one of the following conditions [13]:

- Cognitive delay of more than 2 standard deviations below the mean based on standardised cognitive tests, such as the Bayley Scales of Infant Development II and III [39, 40],
- Moderate to severe cerebral palsy (CP), defined as a score of two or more on the Gross Motor Function Classification System (GMFCS),
- Hearing deficit or loss,
- Severe visual impairment.

The majority of studies of EP infants define moderate to severe NDI as having CP, a developmental quotient (DQ) below 70, and blindness, or deafness [5]. Additionally, behavioural, psychological, and functional outcomes are more and more recognized as important outcomes to evaluate long-term development of EP infants [13].

The GA is an important factor that influences neurodevelopmental outcome. Several studies documented a decreasing risk of NDI with increasing GA [5]. One recent literature review by Jarjour summarized evidence showing that the risk of moderate to severe NDI in infants born in or below 25 weeks of GA is 32% compared to 8% in infants born at 26 weeks of GA [5]. In order to give appropriate and accurate counselling to parents, rates of survival without NDI, or with mild impairment must be considered.

GA als wichtiger Faktor: NDI-Risiko für FG der SSW 25:32 % SSW 26: 9 %

To give estimates of the risk of severe impairment and chances for survival without impairment per gestational week, we identified two SRs that assessed short- and long-term neurodevelopmental outcomes by GA, namely Myrhaug et al., and Moore et al., [1]. In the following section the results from their MAs are presented and quality of evidence and challenges comparing NDI outcome data are discussed.

zwei SRs wurden in Analyse inkludiert

3.2.1 Characteristics of included studies

Short-term neurodevelopmental outcomes

Myrhaug et al. conducted a MA of 10 cohort studies on EP survivors from 1.5 to 3 years of age [1]. The general study characteristics of this SR were described before in chapter 2.2.1.

Kurzzeit-NDI: 1 SR mit MA; inkludiert Daten von 10 Kohorten-studien

To evaluate the risk of impairment, the results from studies that had measured motoric, cognitive and linguistic development at 1.5-3 years of age with Bayley Scales of Infant Development (BSID II and III) or Touwen examination [41] were included in the MA. NDI was categorized as: no impairment (score >85), mild disability (score 70-84), moderate impairment (score 55-69), and severe impairment (score <55) [42]. The studies included by Myrhaug et al. assessed disability with the BSID II or III, and one study [43] used the Touwen examination [41].

aufgrund der Limitationen des BSID Scores wurden 2 MAs berechnet

It is argued that BSID II overestimates and BSID III underestimates functional impairments in children born premature [42]. In order to take into account a potential over or underestimation between the two different versions of the Bayley Scale, two sets of MAs were completed by Myrhaug et al. [1].

We here report data on the rate of survival without impairment and with severe impairment. Detailed outcomes for each gestation week, the rate of disability (none, mild, moderate, severe) and the results of the subgroup analyses of the Bayley Scales II and III can be found in the GRADE summary of findings Table 3.2-3.

Long-term neurodevelopmental outcomes

Langzeitstudien zu NDI: 1 SR mit MA, inkludiert Daten von 9 Kohortenstudien

Moore et al. conducted an SR and MA on long-term outcomes of NDI for EP survivors at GA 22+0-25+6. The review aimed to evaluate if there was a difference in impairment rates with decreasing weeks of gestation [18].

Through a systematic search in MEDLINE and EMBASE they identified 1,771 records, whereby 89 articles were selected for full-text screening, of which 9 studies were included in the final analysis.

Einschlusskriterien des SR

The following inclusion criteria were applied: prospective cohort studies (with or without control group made up from term infants), minimum follow-up rate of 65% or more of survivors aged 4 to 8 years, and use of standardized testing methods to measure NDI. Severe NDI was defined as an IQ score of more than 3 SDs below the mean, non-ambulant CP (GMFCS: 4-5), 'no useful vision', or 'no useful hearing' despite hearing amplification. Moderate NDI was defined as IQ score 2 to 3 SDs below the mean, ambulant CP (GMFCS: 2-3), little useful vision, or hearing restored with amplification.

Daten aus 8 Ländern, Follow-up zwischen 4-8 Jahren

Moore et al., reported outcomes from nine cohort studies that included data from eight countries (France, Norway, United Kingdom, Finland, Australia, Germany, New Zealand, and the Czech Republic). The age of the participants at follow-up ranged between 4 and 8 years, the earliest birth years ranged from 1995 to 1999. Five of the studies included a control group of term infants and three studies had blinded the assessors. All but one study (68%) had a follow-up rate > 78%. In total, 813 preterm survivors were included in the analysis.

Table 3.2-1: Main characteristics of included systematic reviews on neurodevelopmental outcomes

Author, year	Study type	Aim of the study	Intervention/ Exposure vs Comparison	Main endpoints	Inclusion criteria	Exclusion criteria	Included studies (N=52)	Data-bases searched	Search Period	AMSTAR
Moore et al., 2013	SR, MA	To determine the rate of moderate to severe and severe NDI by GA in EP infants followed-up between 4 to 8 years	Exposure: EP (22-25 GA) • Comparison: none or term infants	• Moderate NDI: IQ score 2- 3 SDs below the mean, ambulant CP (GMFCS: 2-3), little useful vision, or hearing restored with amplification • Severe NDI: IQ score >3 SDs below the mean, non-ambulant CP (GMFCS: 4-5), no useful vision, or no useful hearing de-spite hearing amplification	• Population: EP infants born at GA of 22-25 at the age of 4-8 years • Data from high-income countries • Studies: prospective cohort studies, follow-up rate > 65%, use of standardised testing for NDI	• Inadequate quality test, assessments < 4 years, • Follow-up < 65%, • Highly selective cohort, non-cohort study, retrospective cohort study, • Cohort born before 1995, • Unable to obtain data from investigator.	Larroque, 2008, Leversen, 2011, Marlow, 2005, Mikkola, 2005, Roberts, 2010; Stahlmann, 200; Steinmacher, 2008; Woodward, 2009; Zlatohlávková, 2010	Medline, Embase	2004-2013	8
Myrhaug et al. 2017 [1]	SR, MA	To evaluate the prognosis for EP infants who have undergone acute life-saving treatment for a) survival and b) morbidity from discharge	Exposure: EP (22-27 GA) • Comparison: none	• Primary outcomes: survival at discharge, at 1-10 years (see above) • Secondary outcomes: Cerebral Palsy, autism, ADHD, impaired vision, Lung problems, school performance, and/or other health-related outcome. from discharge to home for cohorts and with ≥5 yrs follow-up time for randomized Controlled studies	• Population: EP infants born with a GA of 22-27. • Context: high-income countries, infants born from 1998 until 2015 • Study-design: SR of cohort studies; SR of RCTs, Cohort studies (as of 2000) • Language: English, German, French, Norwegian, Swedish and Danish	• Studies that were not published in full text, • Studies that reported only birth weight, • Studies published before 2000, • Studies from low and middle-income countries, • Studies that only examined prognostic factors and prognostic factor-Models, • RCTs identified via systematic overviews with less than 5 years follow-up time on secondary outcomes.	Boussicalt, 2012; D'Amore, 2011; DeGroote, 2007*; deWaal, 2012*; Kutz, 2009*; Kyser, 2012*; Leversen, 2010; 2011; Michikata, 2010; Moore, 2012; Morgillo, 2014*; Munck, 2010; Nguyen, 2012; Poon, 2013*; Rodrigo, 2015; Schlapbach, 2012*; Serenius, 2013*; Sommer, 2007*; Weber, 2005; Wong, 2014; Zayek, 2011*	MEDLINE, PubMed, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science and CINAHL	2000-June 2015	10

Abbreviations: AMSTAR = A Measurement Tool to Assess Systematic Reviews, RCT = randomized controlled trial, SR = systematic review, yrs. = Years, studies with asterisk were included in the meta-analysis

3.2.2 Findings: Short-term neurodevelopmental outcomes

SSW 22 (22+0-22+6): eingeschränkte Datenlage

For infants born at 22 weeks of GA, only very limited data and results were available for a total of 26 children derived from four studies. It was thus not possible to calculate the rate of survival without impairment. The calculated risk of severe impairment was 37%. Additional calculations and estimations were not possible nor would they be reasonable due to the lack of data [1].

SSW 23 (23+0-23+6): Überlebensrate ohne NDI: 43 %, Risiko für schwere Beeinträchtigung: 26 %

For infants born at 23 weeks of GA, the rate of survival without impairment was 43%. Data was reported by five studies including a total of 58 participants, yet two of the studies only included one participant each at 23 weeks of GA. The risk for severe impairment was 26%. This meta-analysis included data from five studies and 125 survivors.

SSW 24 (24+0-24+6): Überlebensrate ohne NDI: 43 % Risiko für schwere Beeinträchtigung: 20 %

For infants born at 24 weeks of GA, the rate of survival without impairment was 43%. Seven cohort studies included a total of 209 survivors of which 89 had no impairment. One study assessed impairment with the Touwen Score and achieved significantly better results than the other studies, which might be due to the difficulties translating the results from different assessment tools. The subgroup MAs for BSID II and III both showed more coherent and less heterogeneous results, with 35% and 39% respectively. The risk of severe impairment was calculated to be 20% based on all studies including 299 infants, 25% (BSID II) based on 154 infants, and 13% (BSID III) based on 123 infants.

SSW 25 (25+0-25+6): Überlebensrate ohne NDI: 61 % Risiko für schwere Beeinträchtigung: 11 %

For infants born at 25 weeks of GA, the rate of survival without impairment was 61%, and the risk of severe impairments was 11%. These two MAs consisted of 7 studies with 428 children and 8 studies with 485 children.

For infants born at 26 weeks of GA, the rate of no impairment and the risk for severe impairment was 61% and 13%, respectively. Six studies with 572 children reported data on survival without impairment and 7 studies with 604 children reported the risk of serious impairment.

3.2.3 Findings: Long-term neuro-developmental outcomes

Risiko für moderate bis schwere NDI sinkt mit jeder zusätzlichen SSW um 6 %

The results by Moore et al. showed that the risk for moderate to severe NDI significantly decreased for each additional week of GA by 6% (95% CI: 2%-11%) [18]. However, rates for severe NDI did not significantly decrease with successive GA weeks. Regardless of the GA, all EP infants had a considerable risk of developing moderate to severe impairment ranging from 43% to 24%. The rates for moderate and severe impairment for each GA are shown in Table 3.2-2.

Datenlage bei FG der Wochen 22-23 limitiert

Long-term data for infants born at 22 and 23 weeks of GA are limited. Only five out of nine studies reported data on children born at 22 weeks of GA, in total only 12 children were included in the MA. Wide confidence intervals, especially for the lower GAs and a high heterogeneity (I^2>61%) at 24 and 25 weeks of GA limit the results of the MA. The wide confidence intervals might be explained by the small sample size, while the heterogeneous results at higher GA might reflect differences in clinical practice between the different international cohort groups.

Table 3.2-2: Neurodevelopmental impairment of preterm infants at 4 to 8 years

GA week	No. of studies	Risk ratio moderate to severe Impairment in (95%CI)	Risk ratio: severe Impairment (95%CI)
22 GA	5	N=12; 43% (21-69%)	N=12; 31% (12-61%)
23 GA	9	N=75, 40% (27-54%)	N=73; 17% (9-28%)
24 GA	9	N=210; 28% (18-41%)	N=175; 21% (14-30%
25 GA	9	N=441; 24% (17-32%)	N=337; 14% (10-20%)

N = Number of pooled participants; risk rate for moderate to severe/and severe impairment in %; adapted from meta-analysis by Moore et al., 2013

3.2.4 Summary of findings and quality of evidence

Risk of bias assessment

The RoB assessment by Myrhaug et al. [1], was performed with a customized checklist assessing representativeness of study participants, reliable measurement of outcome and exposure (e.g. the method of determination of GA), sufficient follow-up time to detect positive and negative outcomes, drop-out analysis, and blinding of assessors.

Bias-Risiko – mit Checkliste bewertet

Ten studies reported on the outcome risk of impairment of infants born at 22-27 weeks of GA, of which six studies were considered to have a high RoB due to systematic errors assessing impairment.

6 von 10 Studien hatten hohes Bias-Risiko

GRADE

GRADE was used to evaluate the quality of evidence for the risk of experiencing disabilities at birth at the 22-25 weeks of GA measured with BSID II and III at 1.5-3 years [19].

GRADE zur Beurteilung der Qualität der Evidenz angewendet

Table 3.2-3 depicts the summary of findings from the MAs and the sub-analyses. We re-evaluated the quality of evidence and confidence in the effect estimates of the MA using GRADE. We added grading for the survival estimates for 25 weeks of GA, since GRADE analysis was only performed for the weeks 22, 23, and 24 by Myrhaug et al. [1]. We came to different conclusions when grading the quality and confidence of the effect estimates than the authors of the MA. We derived at different conclusions when grading the quality the evidence for survival than the authors of the MA. This was due to the fact that the included studies were cohort studies, and consequently provide 'low quality of evidence'. While Myrhaug et al. started grading at 'high quality of evidence', we concluded that due to the observational study design a lower starting point would be more accurate [19]. However, similarly, we concluded that the certainty of evidence for these outcomes was very low, due to the lack of available data, heterogeneity between studies, and imprecision of the studies. This means that there is limited confidence in the effect estimates and the true effect could be significantly different to the calculated rate.

Qualität der Evidenz sehr niedrig, aufgrund der geringen Fallzahl und hohen Heterogenität der Ergebnisse

We included the results from the subgroup analyses of the assessments with either BSID II or BSID III in the summary of findings table based on Myrhaug et al. [1]. We only reported data where more than 20 patients and more than 2 studies were summarized in a MA. If only single studies reported outcomes, or data existed only for very few patients, evidently, a MA would not be reasonable, thus, we report the number of patients and outcomes.

Subgruppenanalyse für BSID II und III

Table 3.2-3: GRADE summary of findings table of the risk of neurodevelopmental impairment at 1.5-3 years of age

Gestation week	Cognitive Test	Number studies	Number of infants	Rate of disability % (95% CI)				Quality
				None	Mild	Moderate	severe	
22+0 – 22+6 weeks GA	BSID II and III	4[a]	26	1/7 (d.n.s.)	-	2/7 (d.n.s.)	37% (18-56)	⊕○○○ VERY LOW[1, 2, 3]
	BSID II	2	11	-	-	-	4/11 (d.n.s)	
	BSID III	3	15	-	3/7 (d.n.s.)	2/7 (d.n.s)	5/13 (d.n.s)	
23+0 – 23+6 weeks GA	BSID II and III	7	140	43% (17-69)	23% (9-38)	25% (14-35)	26% (5-46)	⊕○○○ VERY LOW[1, 2, 3]
	BSID II	4	57	6/10	5/18	3/18	47% (32-61)	
	BSID III	3	82	14/47[c]	9/47[c]	14/47[c]	12/68	
24+0 – 24+6 weeks GA	BSID II and III	11	352	47% (31-62)	28% (7-49)	26% (20-31)	20% (11-28)	⊕○○○ VERY LOW[1]
	BSID II	6	164	35% (17-53)	2/22[c]	32% (21-42)	25% (10-40)	
	BSID III	3	175	39% (15-64)	45% (21-69)	23% (16-30)	13% (7-19)	
25+0 – 25+6 weeks GA	BSID II and III	10	599	61% (50-72)	23% (10-37)	14% (6-23)	11% (7-15)	⊕○○○ VERY LOW[1]
	BSID II	6	278	60% (45-76)	4/29[c]	15% (8-39)	14% (6-21)	
	BSID III	4	304	54% (34-73)	32% (17-48)	17% (12-22)	9% (5-13)	

Notes: adapted from meta-analysis by Myrhaug et al., 2017; a one study used both BSID II and III and reported data from two cohorts; b one study (Sommer et al., 2007) applied the Touwen tool to evaluate NDI; conly one study reported on this outcome

[1] *(-1) inconsistency: high degree of heterogeneity among studies (I^2 > 90%)*

[2] *(-1) imprecision: broad CIs*

[3] *(-1) studies had a high risk of bias*

keine Bewertung mit GRADE für Moore et al. möglich, da fehlende Bewertung des Bias-Risikos

Moore et al. evaluated study quality by applying pre-defined inclusion criteria, yet did not systematically assess the quality of evidence by using an appraisal tool or GRADE [18]. Since the study did not include a RoB assessment of the included studies, we could not evaluate the quality of evidence for long-term NDI with GRADE.

3.2.5 Challenges interpreting data on neurodevelopmental outcomes

Limitierungen in der Interpretation der NDI Daten:

When comparing study results of neurodevelopmental outcomes after EP birth, it is important to acknowledge the limitations of these data that challenge the interpretation.

- Unterschiede in der Messung und Definition von NDI
- Unterschiede im klinischen Management zwischen verschiedenen Ländern und über die Zeit
- Unterschiede in Förderungsprogrammen und im sozio-ökonomischen Status

Significant differences in results can be related to several reasons, among others, differences in clinical practice (e.g. different limits of viability, differences in clinical management), type of cohorts (single versus multicentre cohort studies), and changes of perinatal practice over time. Furthermore, different assessment tools to evaluate neurodevelopmental outcomes are being used in different studies. One commonly applied tool is the BSID, however, several studies have shown that there are variations in the results of the BSID version II and III, resulting in a potential underestimation of cognitive impairment with BSID III. Several other tools are available, yet not all of them are directly comparable with each other [13].

Studies using different definitions and cut off levels to distinguish between mild, moderate, and severe impairment also challenge comparability of results. Moreover, subsequent confounding factors such as differences in the support and intervention programs could influence neurodevelopmental outcomes and distort results positively or negatively. Development progress of preterm infants is also associated with socioeconomic background: low level of education of the parents and a low socioeconomic status present the major risk factors of developmental disorders [44].

4 Resource utilization and needs of extremely preterm infants

With the rising number of EP infants that have a chance to survive [4], the resource needs to care for these infants are increasing.

Kapitel 4 beschäftigt sich mit Ressourcennutzung und -bedarf für NICUs im Zusammenhang mit FG und GA

In the following chapter, we address resource utilization and resource needs for the care of EP infants in NICUs. In particular, we examined a potential relation of GA and resource utilization/resource needs in NICUs. The chapter aims to provide an overview of the available literature on factors related to resources and infants born at the limit of viability to inform resource planning for NICUs in Austria.

Struktur des Kapitels

We first provide an overview of the current number and future trends of EP births in Austria, their distribution in different regions in Austria, and their characteristics in 2016. Subsequently, we discuss the delineated aspects of resource needs, workforce and hospital capacity, by providing evidence from literature and practise (interviews). Finally, the factors that influence outcomes of EP infants on a hospital and institutional level are presented.

4.1 Trends in number of preterm infants in Austria

20 Jahre Trend der Anzahl an FG in Österreich: 2008: höchster Anteil an FG bisher mit 8.9 %; 2016: 6675 FG; entspricht 7.7 % der Lebendgeborenen

The data retrieved from Statistik Austria (2016) depicts the 20 years trend in the number of liveborn infants by week of gestation in Austria [2].

The trend in the total numbers of preterm infants as percentage of liveborn infants shows a slight decline in the most recent years. The 20 years peak for the total number of preterm infants (22+0-36+6) was in 2008, with 6,928 preterm infants (Table 4.1-1), and a percentage of 8.9% of liveborn infants in Austria. Since then, the number of preterm infants is decreasing (Figure 4.1-1 and Table 4.1-1). In 2016, the percentage of preterm infants was at a new low with 7.7% percent, and in absolute terms, 6,675 infants.

The absolute numbers of preterm infants of the past 10 years in relation to all liveborn infants in Austria are presented in Table 4.1-1.

Europa: große Unterschiede in der Anzahl an FG zwischen 5 % und 10 %

Similar trends of a recent decline in the percentage of preterm infants were seen in other countries [15]. For example in the US, the percentage of preterm births peaked in 2006 with 12.8% of births, and is steadily declining since then [45]. In Europe, there is wide variation of 5 to 10% in preterm births rates. Until 2008, overall preterm birth rates and multiple preterm birth rates increased in most countries, yet singleton preterm birth rates decreased or remained stable [15].

FG der Wochen <28, <32 und <34 umfassen den kleineren Anteil der FG mit insgesamt 2 %; 5-6 % der FG sind >34 Wochen geboren

Infants born EP (<28 weeks), early (28+0-31+6) or moderate (32+0-33+6) comprise the smallest proportion of births: In 2016, they accounted for 0.4%, 0.7%, and 1% respectively. Most preterm births occur in the late preterm period of 34+0 to 36+6 weeks, accounting for 5.6% of all births in 2016.

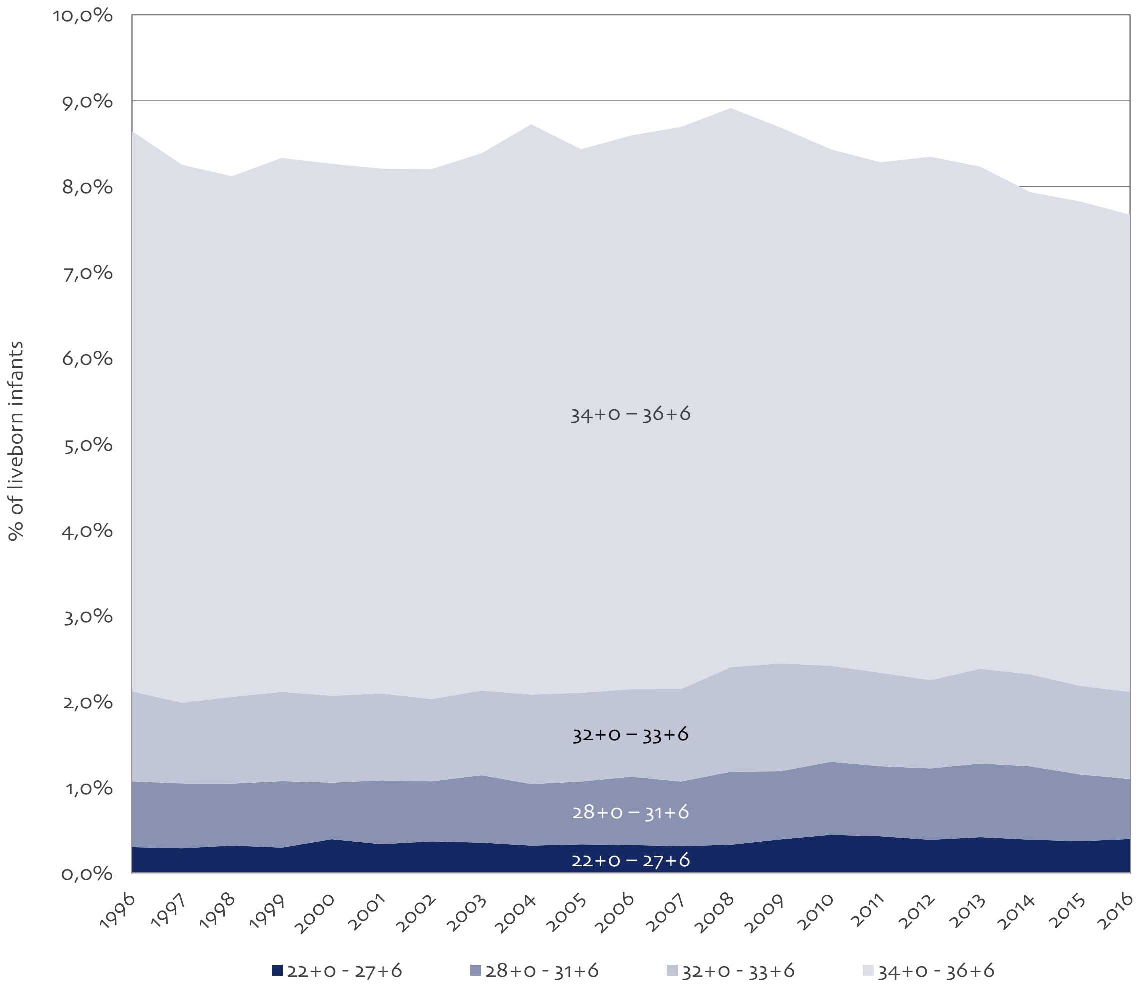

*Figure 4.1-1: Trend of the number of preterm infant as percentage of liveborn infants in Austria from 1996-2016. Data adapted from Statistik Austria [2]; *1995-2010: revised data regarding lengths of pregnancy*

Table 4.1-1: Absolute numbers of preterm and liveborn infants in Austria 2006-2016 [2]

Year	Liveborn infants	Preterm births				
		total	22+0-27+6	28+0-31+6	32+0-33+6	34+0-36+6
2006	77,896	6,694	257	620	794	5,023
2007	76,232	6,627	242	573	821	4,991
2008	77,728	6,928	259	661	947	5,061
2009	76,322	6,628	302	606	958	4,762
2010	78,698	6,637	353	669	881	4,734
2011	78,080	6,466	337	637	850	4,642
2012	78,924	6,587	308	656	812	4,811
2013	79,294	6,526	334	681	875	4,636
2014	81,676	6,480	320	698	875	4,587
2015	83,607	6,542	313	650	862	4,717
2016	87,018	6,675	348	608	883	4,836

The number of EP infants remained relatively steady over the past 20 years, ranging from 0.31% in 1996 to a maximum of 0.45% in 2010. The absolute numbers of early and EP infants over the past 20 years are depicted in Figure 4.1-2. From 2007 to 2010, the number of EP infants increased by 100 infants from around 250 to 350 infants. In 2016, 348 infants were born extremely preterm, and 608 infants were born very early. Liveborn infants born before 22 weeks of GA are not shown in the figure, but accounted for 38 infants in 2016 [2].

in 2016 wurden 348 Säuglinge <28 Woche geboren, 608 Säuglinge <32 Wochen und 38 Säugling <22 Wochen

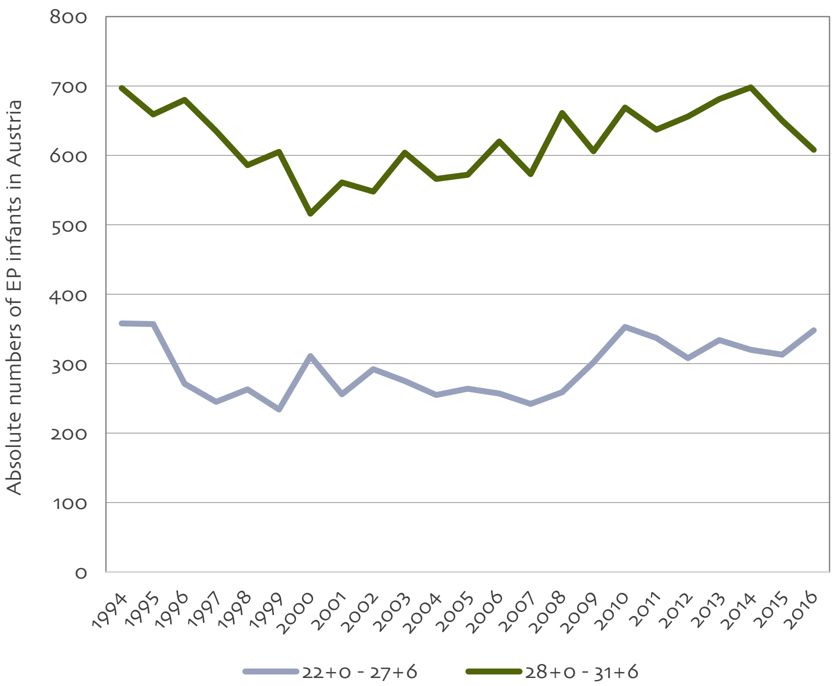

*Figure 4.1-2: Absolute numbers of extremely preterm and very early born children as proportion of liveborn infants in Austria; Data adapted from Statistik Austria [2] *1995-2010: revised data regarding lengths of pregnancy*

4.1.1 Regional distribution of preterm and extremely preterm births

In 2016, 1,500 preterm infants were born in Vienna, of which 125 were extremely preterm, 145 early preterm, and 177 moderate preterms; the majority were late preterm infants with 1070 births in 2016. Apart from Vienna, Lower- and Upper Austria have more than 1100 preterm births per year. Burgenland[3], Carinthia, Salzburg, and Vorarlberg have less than 400 preterm births in 2016, and less than 20 EP infants. Figure 4.1-3 depicts the distribution of preterm births in the federal state of Austria in absolute numbers.

2016:
Wien: 1.500 FG, davon 125 <28 Wochen
Niederösterreich und Oberösterreich: >1100 FG, davon 60 < 28 Wochen

[3] Burgenland has no NICU clinic, which explains the low number of EP and preterm births. These infants should be transferred to clinics in Graz or Vienna.

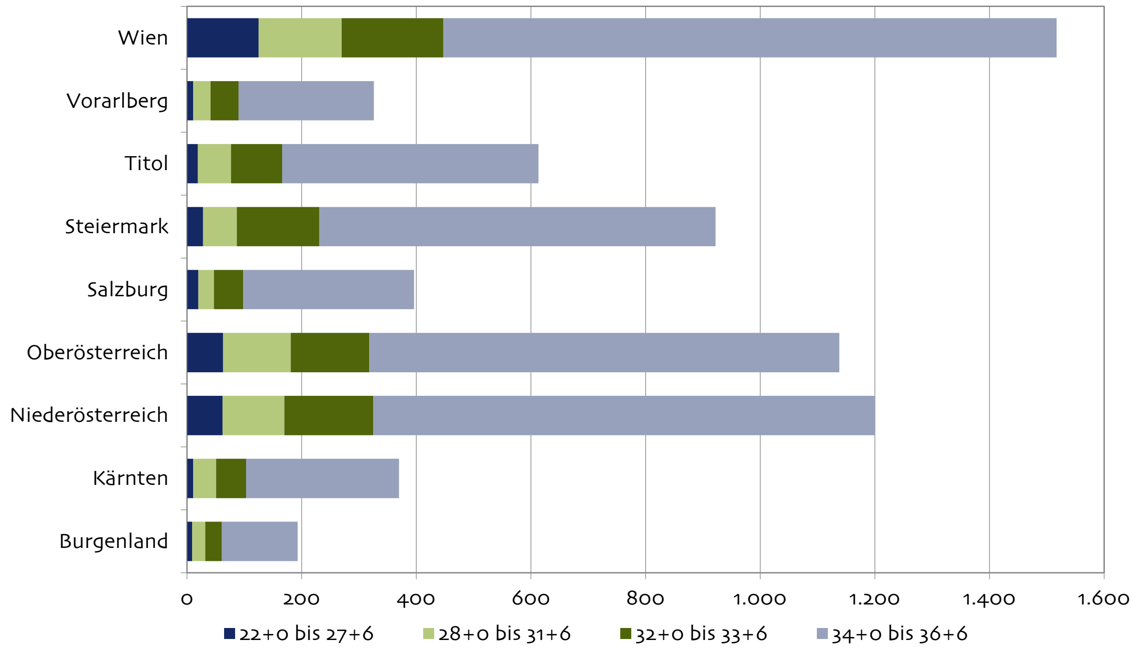

Figure 4.1-3: Number of preterm births per federal state in Austria, 2016; Data adapted from Statistik Austria [2]

absolute Zahlen der EFG per Bundesland geben Auskunft über Auslastung und Routine im Umgang mit EFG

In relation to the total number of births per region, preterm births, and EP births in Austria are evenly distributed. Only Burgenland, Styria, and Tyrol have relatively more preterm births in relation to normal births (difference less than 1%) and Vienna has slightly more cases of EP births as percentage of all births (difference less than 0.2%) (Data not shown).

Anzahl der FG in Österreich gleichmäßig über Bundesländer verteilt

Absolute numbers of EP infants provide insights into the probable occupancy rate in NICU clinics and the level of routine that clinics can get when caring for infants at the limit of viability. Figure 4.1-4 shows the number of EP infants per federal state in 2016. In Vienna, most EP infants were born with a total number of 125 births, followed by Lower-Austria, and Upper Austria with 62 and 63 EP births respectively. Burgenland has the lowest absolute number of EP infants with 9 births in 2016.

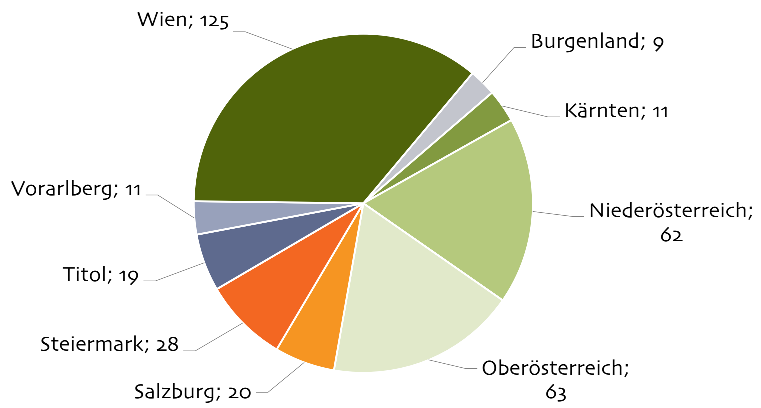

Figure 4.1-4: Distribution of extremely preterm births in Austria, absolute numbers of extremly preterm infants per region in 2016; Data adapted from Statistik Austria [2]

4.1.2 Characteristics of extremely preterm births in 2016

The large majority of preterm infants were born between at 32+0 and 36+6 weeks of GA, accounting for 85% of preterm infants (Figure 4.1-5a.). 5% of all preterm infants were born between 22+0 and 27+6 weeks of gestation. The four pie charts in Figure 4.1-5 present characteristics of births at the limit of viability in Austria in 2016.

2016: Großteil (85 %) der FG zwischen 32 und 36 SSW geboren, nur 5 % der FG waren EFG

From all EP infants born in 2016, nearly a quarter of infants were multiples and three quarters were singleton births. 70% of the EP infants have the Austrian citizenship, 12% come from other EU states, and roughly 20% have a nationality outside the EU. The age distribution of mothers at the time of delivery shows a heterogeneous picture: one-third of mothers are between 30 and 34 years old at the time of delivery; one-quarter of mothers are between 25 and 29 years old, and a fifth of mothers are between 35 until 39 years old.

¼ der EFG waren Mehrlinge; 70 % hatten österreichische Staatsbürgerschaft; Alter der Mutter uneinheitlich

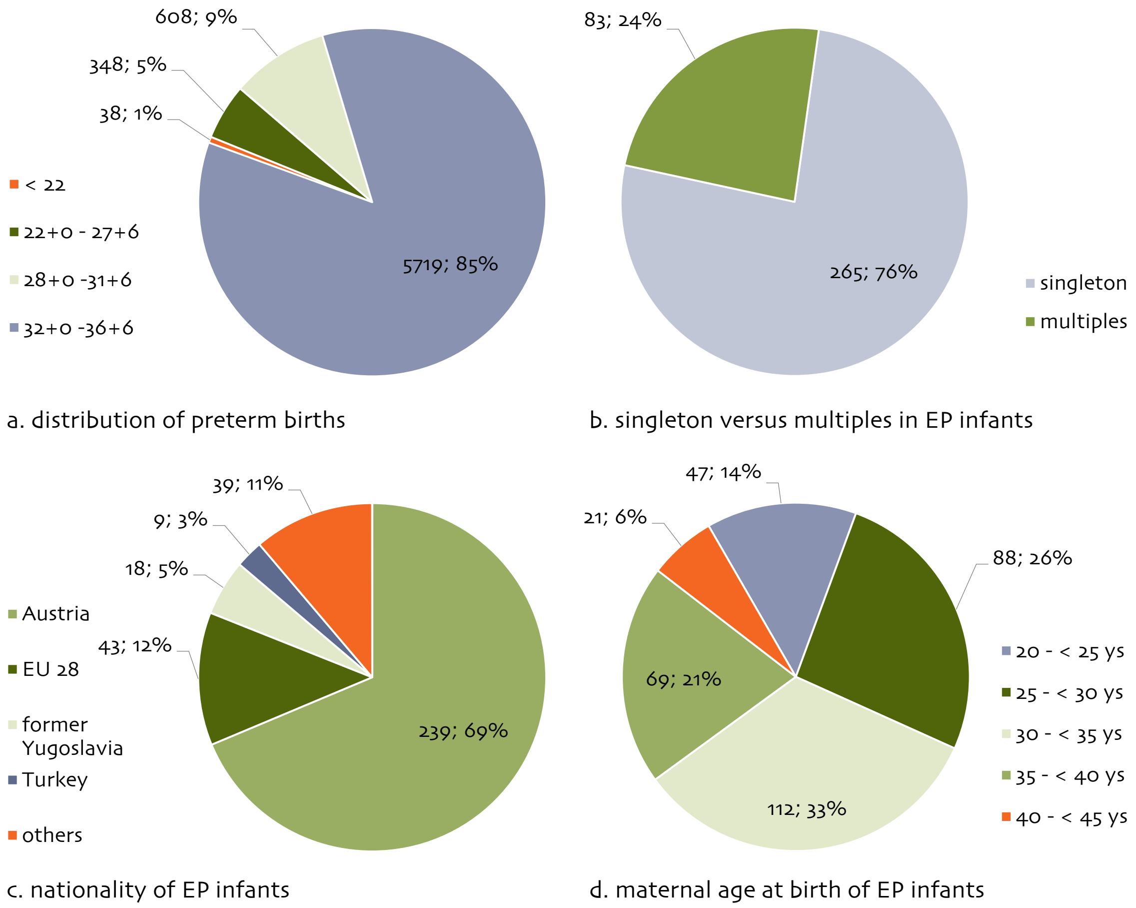

Figure 4.1-5: Characteristics of extremely preterm births in 2016, (absolute numbers and; percentage) Data adapted from Statistik Austria [2]; EP = extremely preterm, ys = years;

4.1.3 Reported current- and predicted future trends for EP births in Austria

kein Anstieg der Anzahl an FG, laut Interviews

Interview participants were asked whether they currently experience an increase in the number of preterm infants and, in particular, EP infants. An increase of preterm infants was negated by all interviewees.

Wien: Zahl der moderaten und späten FG sinkt, Anzahl der EFG steigt leicht

Graz: Zahl der späten FG steigt, zusätzlich: Überleben der EFG verbessert, dadurch erhöhter Ressourcenbedarf

In between the different age groups of preterm infants, divergent observations were made by interviewees: In Vienna, a decrease in the moderate and late preterm birth group and a trend towards an increase in extremely premature infants was noted. In Graz, rather than the number of EP infants, the number of late preterm infants, above a GA of 32 weeks seems to be rising. Since late preterm infants account for a higher percentage of preterm infants, this rise leads to a noticeable increase of resource needs in terms of manpower. Very preterm infants, on the other hand, stay longer in the hospitals, since survival has improved. The higher numbers of later preterm infants (32+0- 36+6), combined with the improved outcomes of EP infants result in a higher resources demand.

> *'… This is a very complex topic. It's definitely an increased need at the moment, you can see that all over Europe. But it's a mixture of different reasons why. One thing is that we have an increased number of late preterm infants. In the group of infants above 32 weeks of gestation, we have a huge increase in numbers. And they really cover a lot of our manpower, because of the high number (…) and on the other hand, we have infants with very low gestational age of 23, 24, 25 weeks. These infants are not really increasing a lot in numbers, there are not many of them, but these infants need more resources every year because they stay longer in the NICU. With 23 weeks you will stay 17 weeks in the NICU.'*
> (Urlesberger, NICU Graz)

steigende Anzahl der Zwillings- und Mehrlingsgeburten; 60 % der Mehrlingsgeburten sind FG

Rising resource needs for late preterm infants were also associated with an increase in twin and multiples deliveries by some of the interviewees. 60% of the multiples born in 2016 were born prematurely [2]. The probability of twin deliveries rises with maternal age and with the utilization of artificial productive technology (ART), such as in vitro fertilization (IVF). The percentage of IVF births is not known, and can only be estimated as this information is provided on a voluntary basis.

Anzahl der IVF Geburten nicht bekannt; AKH Wien schätzt 15 % der FG IVF Geburten

In the AKH, Vienna, around 15% of preterm infants were estimated to be IVF births. The head of the NICU, AKH Vienna, explained that in the last year, around 50% of infants born < 32 weeks were multiples, which is also associated with IVF births. However, since the AKH is a specialized centre for multiples, the share of IVF might be higher than in other clinics:

> *'We have this focus on multiples, and many of those [EP infants] are multiples. I don't know the data from last year but 2 years ago, we had 50% multiples. So, this is also not the normal distribution, it's quite a specialized patient population.'*
> (Berger, NICU AKH, Vienna)

Migration und demographische Veränderungen könnten zukünftig zur Anstieg der FG Anzahl führen

Migration and demographic changes were mentioned as unknown variables that could potentially lead to an increase of EP infants in the future years, especially in Vienna.

4.2 Health Personnel and workforce in NICUs

Workforce and health personnel of NICUs was identified as one of the key aspects when it comes to improving the outcomes of EP births confirmed both by the literature [46-50] and interviewees.

Personal und Belegschaft hat entscheidenden Einfluss auf Behandlungserfolg laut Literatur und Interviews

4.2.1 Findings from literature

We could identify several publications that analysed the relation of health personnel, in particular, nurses, to outcomes of EP infants in NICU clinics. A summary of the characteristics, context and main findings of identified publications are presented in Table 4.2-1.

Table 4.2-1: Summary of identified publications: relation of nurse workforce to NICU outcomes

Titel	Study Design	Included Infants/ Participants	Primary Outcome/ Issue	Context	Conclusion
Sherenian et al., 2013 [46]	SR (N=5, Callaghan et al.; Hamilton et al., Cimiotti et al., Granid et al., Profit et al., Tucker et al.)	19570* patients admitted to NICUs Studies with varying number of infants	Mortality before discharge relative to NPR	International, NICUs from UK, USA, Australia, South America	NPR affect outcomes of NICUs; Limitations in data and comparability
Rogowski et al., 2013[47]	Retrospective cohort study	11401VLBW infants 67 US NICUs (VON)	Nurse Staffing and NICU Infection Rates – adequacy of NICU nurse staffing in the United States	USA	Widespread nurse understaffing relative to national guidelines; understaffing associated with increased risk of nosocomial infections
Rogowski et al. 2015 [48]	Cohort study	15191 infants 6038 nurses 104 NICUs	NPR at each acuity level[4], factors other than acuity, including nurse qualifications, the availability of physicians that determined staffing ratios;	USA	Staffing ratio significantly related to acuity of assigned infants, but not to nurse education, experience, certification, or availability of other providers
Gagliardi et al., 2016 [52]	Cross-sectional observational survey	11082 infants 756 nurses 63 NICUs (INN)	Acuity-adjusted NPR in Italien NICUs	Italy	Moderate understaffing of Italien NICUs
Sink et al., 2010 [53]	Retrospective cohort study	14 infants <29weeks GA 87 nurses 1 NICU	Relationship of number of infants assigned to NICU nurses and oxygen saturation in premature infants	USA	Fewer patients per nurse associated with improvement in oxygen saturation
Lake et al., 2015 [50]	Retrospective cohort study and survey	85252 VLBW infants 5773 nurses (VON)	Relationship of poor hospital nursing characteristics with hospital-level disparities in VLBW infant outcomes	USA	Poorer nursing characteristics contribute to disparities in VLBW infant outcomes in two nurse-sensitive perinatal quality standards

[4] Definition for infants' acuity level, i.e. level of care provision needed for each infant defined by acuteness of care provision, from [52].

Titel	Study Design	Included Infants/ Participants	Primary Outcome/ Issue	Context	Conclusion
Lake et al., 2012 [49]	Cohort study	72235 VLBW infants (VON)	Relationships between hospital RNE and VLBW infant outcome	USA	Significantly lower risk-adjusted rate of 7-day mortality, nosocomial infection, and severe intraventricular haemorrhage among VLBW infants born in RNE hospitals, not of 28-day mortality or hospital stay mortality
Party et al., 2014 [54]	Prospective cohort study	University clinic in Germany	Nurse staffing requirements for NICUs following new staffing rules based on BAPM criteria and actual availability of nurses	Germany	Average nursing staff requirement was 12 FTE per shift; actual nursing availability was 9 FTE; ICU seems understaffed if new nursing requirements are applied

*Notes: *5296 very low births weight infants; BAPM = British Association of Perinatal Medicine; FTE = full time equivalent; INN = Italian Neonatal Network; NICU = Neonatal intensive care unit; NPR = Nurse-to-patient ratio; RNE = Recognition for nursing excellence, VLBW = very low birth weight infants; VON = Vermont Oxford Network;*

SR zum Zusammenhang der NPR und des Behandlungserfolgs: primäres Ziel: Überleben in Zusammenhang mit NPR in NICUs

One SR focused on the relation of the nurse to patient ratio (NPR) to patient outcomes. The primary outcome was mortality at discharge relative to NPR [46]. The review analysed results from five studies including 19,570 patients from NICUs in the UK, USA, Australia and South America. The patients were not limited to preterm infants or EP infants, however, three of the included studies focused specifically on very low birth weight infants. The quality of evidence is considered low, due to a high degree of inconsistency between studies, and a high heterogeneity.

Ergebnisse: Unterschiedliche Definitionen und Berechnungen der NPR limitiert internationalen Vergleich

unklar in wie fern NPR das Arbeitspensum widerspiegelt

The authors criticised that each of the studies defined and calculated the NPR in different ways. For instance, as average of total staff divided by total infants for each shift during the first 72 hours of administration, or as average daily census divided by number of nurses [46]. Furthermore, different cut off levels were used to distinguish high, medium, and low ratios of NPR. Consequently, no MA could be calculated. While limited by the available data, their results showed that NPRs in NICUs might have a measurable effect on outcomes. The authors concluded that the limited possibilities to define and quantify *workload* in a coherent way across institutional and organisational settings results in research that depends on the NPR to predict nursing intensity and workload. However, it is unclear to what extent the NPR is reflecting the workload of nurses on NICUs and the requirements for nurse staffing [46].

identifizierte Primärstudien zu Personal und NICUs hatten unterschiedliche RQ und Ziele; Ergebnisse lassen sich nicht auf Österreich übertragen

The identified primary studies had very heterogeneous research questions and primary objectives. The applied methods were relatively similar (mostly retrospective cohort studies and nurse surveys), however, the studies originated from different contexts and settings that made the direct comparison of results difficult. The findings of the publications are not necessarily applicable to the Austrian context, since responsibility and tasks of NICU nurses differ between countries, and in particular in the US [48, 54].

There is scarcity of international data on the nurse workload and countries have diverging perceptions and methodological approaches towards a defined NPR. Reports on the understaffing of NICUs, however, seem to present the common denominator of international evidence:

gemeinsamer Nenner: Unterbesetzung der NICUs, ins besondere bei Pflegepersonal

- In the US, where nurse ratios and staff rules have been developed since 1992, significant nurse understaffing relative to national guidelines has been reported and associated with increased infection rates for EP infants [47]. In the US, the NPR is defined by patients' acuity level according to guidelines for perinatal care, which categorises the level of acuteness and interventions an infant needs. Infants with acuity level 3 to 5 require intensive care, whereby acuity level 5 would require a NPR of >1:1, level 4 an NPR of 1:1, and level 3 an NPR of 1:1-2.

USA: signifikante Unterbesetzung im Vergleich mit nationalen Guidelines führte zu erhöhten Infektionsraten für EFG

- In the UK, nurse ratios are applied according to the criteria provided by the British Association of Perinatal Medicine (BAPM), defining different levels of care categories that require different NPRs [55]. The BAPM comprises 4 categories, intensive care, high dependency care, special care and transitional care. For infants in need of intensive care (category 1), a 1:1 NPR is required. Two prospective studies suggested considerable understaffing in UK based tertiary hospitals, reporting 54% and 57% respectively of nurse shifts that failed to meet BAPM standards [56, 57]

UK: NPR nach BAPM Kriterien, 1:1 NPR für EFG in Intensivpflege

2 prospektive Studien zeigten das 54-57 % der Pflegeschichten unterbesetzt sind

- In Germany, nurse staffing rules according to the BAPM criteria were introduced recently, in 2014, requiring a ratio for patients with a birth weight below 1,500 gram. According to the criteria, a 1:1 NPR is required for infants in need of intensive care and a 1:2 NPR for infants in need of monitoring. An initial evaluation conducted by the University hospital of Heidelberg suggested a gap between the average nursing staff requirements according to a 1:1 NPR (on average 12 full-time equivalents per shift) and actual nursing availability (9 full-time equivalents per shift) [54]. Furthermore, they emphasised the need to consider other paediatric patients apart from intensive care patients in nurse ratios, which is not the case in the current requirements.

Deutschland: seit 2014 NPR laut BAPM Kriterien; erste Evaluierungsstudie zeigt Lücke zwischen NPR Vorgaben und tatsächlicher Personalverfügbarkeit

While strict ratios present a simple measure to determine staffing levels, their main weakness is their potential inflexibility and inefficiency if they do not accurately reflect the workload [58]. Due to the difficulties of quantifying the workload, Sherenian et al. suggest developing tools to measure nurse satisfaction, expertise, and stress, and evaluate if and how these factors correlate with concrete factors such as patient-level outcomes (infection rates and mortality) and occupancy rate. They further recommend identifying factors that maximize the quality of neonatal nursing care rather than just identify the maximum workload a unit can bear without affecting outcomes and causing harms [46].

Nachteil einer NPRs sind fehlende Flexibilität und potentielle Ineffizienz

statt maximaler Arbeitslast sollten maximale Qualitätsfaktoren gemessen werden

4.2.2 Findings from interviews: Perspective on workforce

Nurse-to-Patient ratio

In Austria, the ratio of nurses in NICUs is 1:2.5 and relates to the number of nurses per intensive care bed for 24 hours, i.e. one intensive care bed should be covered by 2.5 nurses. This ratio is understood as a recommendation and is not binding. In comparison to the BAPM criteria that recommend a 1:1 patient to nurse ratio (per nurse shift), the bed to nurse ratio takes into account that one nurse is not available for 24 hours, explained the interviewees.

Österreich: pro Intensivbett 2,5 Pflegekräfte per 24 h

'We have to be very careful if we talk about ratios: do you mean intensive care places versus nurses? Or do you mean a 1:1 nurse situation in high-risk patients. This is getting mixed up very often. For each of the local intensive care places there are 2.5 nurses, but we can switch to 1:1 nursing on demand.' (Urlesberger, NICU Graz)

AKH Wien und Linz streben 1:3,5 Ratio an, deckt allerdings Ressourcenbedarf nicht ab

In the AKH, Vienna and in Linz, a ratio of 1:3.5 for neonatal intensive care beds is targeted. Both interviewees shared their concern that this does not cover the need and is not always achieved:

'... we have established a 1:3.5 ratio for our neonatal intensive care beds, but even this is not enough. This means: if we have a ward with 10 beds, we need 35 full-time nurses in order to run it. This makes a presence of 5 nurses in the night, so during the night, 1 nurse has to care for 2 babies; and during the day it's a little bit more, so we have like 6 nurses there ... so we have 1 or 2 who have only 1 patient, that's mostly the sickest one, and the others are caring for 2 also during the day.' (Berger, NICU AKH, Vienna)

Shortages of nurses

Engpass an Pflegekräften aufgrund niedriger Attraktivität des Arbeitsplatzes, hoher Arbeitslast, und Mangel an ausgebildeten Fachkräften

In relation to resource needs, several interviewees stressed a pressing 'shortage of nurses'. The interviewees mentioned several underlying reasons: limited funding for further nurse placements, low attractiveness of the workplace due to a higher workload, and lacking availability of trained paediatric nurses. While in some clinics one of these factors is predominant, a combination of the three seems to be the common reason for the shortage, according to the interviews. The limited number of nurses often results in closed beds and limited capacity at NICU clinics. Furthermore, a shortage of nurses can also influence the outcomes and lead to an increase of infections and adverse events.

Mangel an Pflegekräften hat Auswirkungen auf Infektionsraten und Komplikationen

Four of the interview participants reported having closed beds as a consequence of a lack of nurses at the time of the interview. Table 4.2-2 summarizes the perspective of the interviewees on the situation of nurse workforce in the five NICU clinics.

Table 4.2-2: Perspectives on nurse staff from five perinatal centres in Austria

Theme: health personnel and workforce		
Perinatal center	Code: Nurse staff	Identified key challenge
NICU, AKH, Vienna	*'Since I have been working here, we always had a lack of nurses! We always had beds closed although it was always a shortage of beds, yet we always had some that were closed because we did not have enough nurses.'*	Education and training of new nurses Workload for nurses
NICU, Graz	*'... we realized that we have a shortage of nurses. But this was about 6 to 8 years ago and we doubled our school numbers so at the moment we don't have really a problem in nurses in Styria.'*	Currently no challenge, but future prospect of potential shortage
NICU, Innsbruck	*'At the moment 2 of the intensive care beds are closed and 2 intermediate care beds, because we do not have enough nurses. (...) I think several NICUs have closed beds, because of staff problems...'*	Education and training of new nurses
NICU, Linz	*'I don't know any centre in Austria which has enough nurses for their babies ....'*	Financing of additional positions
NICU, Salzburg	*'That's a real problem, because in the last years, all over the wards they reduced the nurse staff in the neonatal ward, and they see that the infection and the mortality is rising. And in the last years in Germany, there was a change in the law so that they need higher staff count. In Austria, only Vienna has nearly the same staff count that they now need in Germany. Our staff count was lower in the last years, so we have a big problem with infections so that I closed 4 beds on my ward.'*	Attractiveness of the workplace Financing of additional positions Lack of staff associated with rising adverse events (infections)

One key aspect particularly emphasised by several interviewees was the limited training courses and a low number of nurses in training to become paediatric intensive care nurse. In the past years, the training education for paediatric nurses was stopped to be changed to a bachelor curriculum in line with EU requirements. The head of the NICU AKH, Vienna, expects that this will aggravate the shortage of nurses in the near future:

geringe Zahl an Ausbildungsplätzen und fehlende ausgebildete Pflegefachkräfte als Hauptproblem

> *'The problem is definitely that there are not enough nurses trained (...) From 2013 onwards, we had 60 young pupils starting training every year until 2016. We had 2 cohorts of 60 nurses who started, so it was like 50 or 52 who finished. And still, we didn't have enough because we were always increasing our beds and other hospitals too since the number of inhabitants in Vienna increased. They had to open more and more beds, so although we had these two cohorts we did not have enough nurses. And now, since 2016, no training course started, because the curriculum is changed to a bachelor system (...) So we will definitely have a huge problem in 2019/2020 because we're missing those double cohorts that we had trained so far.'* (Berger, NICU AKH, Vienna)

durch die Umstellung in ein Bachelor Curriculum

könnte sich die Ausbildungsdauer für Pflegekräfte verlängern

und

zu einem Pflegekräfteengpass 2019/2020 führen

This issue was shared by the other interviewees emphasising the limited number of trained paediatric and intensive care nurses available:

> *'I'm convinced that we need more nurses. There should be more nurses educated and motivated to work in NICUs. Education is one of the challenges.'*
> (Kiechl- Kohlendorfer, NICU Innsbruck)

Furthermore, within the new curriculum, the professional training for paediatric intensive care nurses takes longer. Trainees will first have to undergo three years of general traineeship before adding one year of specializations to become a paediatric nurse or an intensive care nurse.

> *'... it takes too long time, because if you have the general training first and then the intensive care training, it takes 4 years of education and several additional years of training until they really can work with the same experience that they are having now ...'* (Berger, NICU AKH, Vienna)

Only one of the interview participants negated the current shortage of nurses, which is explained to be the result of an agreement with medical CEO responsible for nurse training. However, the interviewee shared the concern of his colleagues that the number of nurses could become critical again in the future, due to a change in the training curriculum for nurses by 2020.

Medical doctors

While the heads of the NICUs face similar challenges to meet their staffing requirements for nurses, the clinics reported deviating issues in relation to the number of medical doctors:

unterschiedliche Probleme in Bezug auf ausreichende Stellen für NeonatologInnen an NICU Kliniken

Two interviewees stated that shortage of workforce was limited to nurses only and that they have sufficient physicians' workforce in their units. Three interviewees expressed that they experienced a deficit of medical doctors due to the introduction of the maximum workhour regulation of 48 hours.

2 Kliniken: Personalengpässe nur in Bezug auf Pflegekräfte

In contrast to the other NICU clinics, Graz reported to have a sufficient amount of nurses, yet, they face challenges when it comes to medical doctors. Following the introduction of the 48 working hours per week, placements for medical doctors were not sufficiently filled to make up for the time loss of working hours. Similarly, the NICU of the AKH, Vienna reported difficulties to have a sufficient number of medical doctors available to cover all of their shifts. However, due to an exemption regulation for University hospitals allowing medical doctors to work 55 hours in research and practice, this was not considered as

3 Kliniken: Engpässe in Belegschaft aufgrund des Arbeitszeitengesetzes und Schwierigkeiten in der Nachbesetzung ausgeschriebener Stellen

the most pressing aspect in terms of NICU workforce. Furthermore, in the AKH, Vienna, most neonatal paediatricians choose to opt-out of the 48-hour week regulation. Apart from problems to meet the requirements of the regulation on maximal working hours for medical doctors, the NICU Innsbruck reported to faces challenges to fill their vacancies. However, this shortage in physicians' workforce did not influence the number of available beds, so far, the interviewee noted.

Doctors-to-Patient ratio

keine Literatur zu einer empfohlenen ÄrztInnen-Quote für NICU Klinken

No literature on issues related to the doctor-to-patient ratio was identified in the systematic search or hand search. In order to assess this topic for Austria, it was included in the semi-structured interview guide and asked the experts. According to the interviews, there is no specific doctor-to-patient ratio in Austria. The perinatal centres are complying with the ÖSG 2017 – the Austrian structural plan for healthcare management, which provides quality criteria to be fulfilled, such as the number of specialised doctors present per shift (one paediatrician per NICU shift) and the numbers of specialised doctors per unit (two paediatricians) [59].

4.3 Hospital capacity for extremely preterm infants

4.3.1 Findings from literature: Length of stay in relation to gestational age

vermehrter Bedarf an Langzeitspitals-aufenthalten mit erhöhtem Arbeitspensum durch steigende Anzahl überlebender FG

The improvement of neonatal care with the increasing number of EP infants surviving has also led to a rise in the number of infants requiring long-term neonatal care. Consequently, the workload within NICUs and the total number of days in clinics increased.

A prediction of the length of stay (LOS) for EP infants can facilitate resource planning for neonatal intensive care as well as it helps in counselling of parents and in managing their expectations.

Characteristics of studies

zum Thema Krankenhausaufenthalts dauer (LOS) wurde 1 SR gefunden, der sich mit der Vorhersage der LOS bei EFG beschäftigte

We could identify one SR that focused on factors predicting LOS in NICUs [60]. In addition, five primary studies were found [61-65], which were also included in the SR by Seaton et al.[60]. The contextual background of the studies were NICU departments in the UK and the US. From an overall search of 5,042 publications, Seaton et al. could identify nine relevant studies estimating the LOS in neonatal clinics. Out of the nine publications analysed, five specifically focused on early or EP born infants. Table 4.3-1 provides an overview of the characteristics of the SR and the included primary studies on the LOS of EP infants.

Findings

The SR summarized 39 prognostic factors mentioned in the included studies to estimate the LOS. The authors categorized the factors into broad areas, namely

in 9 Publikationen wurden 39 Faktoren gemessen um LOS zu prognostizieren, Faktoren wurden 5 Kategorien zugeordnet

- inherent factors,
- antenatal treatment or maternal factors,
- conditions of the infants,
- treatment of the infants, and
- organisational aspects.

Inherent factors, such as births weight, congenital malformations, GA, head circumference, etc. were considered by all studies since these factors provide the advantage of being simple and objective to measure and available at birth. However, the choice which inherent factors were considered relevant for a prediction of the LOS differed significantly in between studies. For instance, the factor birth weight was considered by 8 out of 9 studies, but only 3 studies considered congenital malformations, 3 studies considered ethnicity/race/nationality and only 5 studies considered sex. For other categories, this variance was even more pronounced. For instance, while seven studies considered factors related to *the condition of the infant* as relevant factor to predict the LOS, only two studies chose the identical factors (Apgar score and SNAPPE-II).

inhärente Faktoren wurden in allen 9 Studien berücksichtigt, allerdings gab es starke Unterschiede in der Auswahl dieser Faktoren (Geburtsgewicht, GA etc)

bei den weiteren 4 Kategorien waren diese Unterschiede noch stärker

Organisational factors were considered by five studies, however, these factors are highly limited to their contextual setting. For instance, Manktelow et al. found that apart from birth weight and GA, which had the strongest influence on the LOS, the initial reason for admission and the need for respiratory support in the first 12 h showed the most consistent association to the LOS [61]. Testing their model on different NICU units in the UK showed significant variances to the predicted LOS, irrespective of unit size and case-mix.

organisatorische Faktoren waren zudem auf den Kontext limitiert

Seaton et al. concluded that based on the inherent factors birth weight, sex, and GA, an initial estimation of the LOS can be made [60]. While inherent factors provide information from the first day of life and are simple and objective to measure, the prediction is likely to change over time depending on the progress of the infant and quality of care, and a revision would be needed to get to a more accurate estimation.

anhand von inhärenten Faktoren könnte die initiale LOS prognostiziert werden, die allerdings stark von tatsächlicher LOS abweichen kann

Limitations and Conclusions

Seaton et al. emphasised on the limitations of the applicability of study findings due to the high variance in between studies and factors considered to estimate the LOS [60]. In particular, the use of organisational factors to predict the LOS would limit generalizability to other settings, as these aspects could differ from unit to unit, even within countries. Consequently, the authors suggest that future predictions on the LOS should avoid organisational aspects and allow generalization. Furthermore, the authors proposed to choose a simple, pragmatic approach to ensure clinical applicability of a prediction of the LOS[60].

Limitierung der Studie sind fehlende Übertragbarkeit, aufgrund der hohen Varianz an Faktoren um LOS zu berechnen

Table 4.3-1: Characteristics of studies estimating length of stay of EP infants

Author	Year of publication	Included studies	Quality appraisal	Exclusion criteria	Context	Conclusion
Seaton et al.	2016	9 (5 on EP infants)	Yes; Quality In Prognostic Studies	Conference proceedings, Review articles, letters and editorials, Countries outside the OECD, Clinical trials, Wrong study population, Specific disease areas, Work that was subsequently updated or validation studies.	UK	Lack of evidence to accurately estimate LOS, inherent factors (birth weight, sex, and gestational age) allow simple, objective LOS estimation
Included primary studies	**Year of publication (data)**	**Included patients**	**Patient population**	**Exclusion criteria**	**Context/setting**	**Conclusion**
Hinchliffe et al. [65]	2013 (2006–2010)	2723	24–28 weeks GA	Ambiguous sex; implausible birth weight.	The UK,	Discharge of alive infants occurred over a longer period for lower GA and smaller birthweight infants
Hintz et al. [63]	2010 (2002–2005)	2254	<27 weeks GA	Congenital anomalies; in hospital >1 years; transferred to long-term care.	USA, NICHD Unclear but likely to be NICU due to GA	Prediction of discharge is poor if only perinatal factors are considered. Predictive models that use a few key risk factors are comparable to the full models; offer a clinically applicable strategy.
Lee et al. [62]	2013 (2008–2010)	2012	401–1000 g birth weight	Congenital anomalies; death; surgery.	USA, NICU	Lower birth weight, lack of antenatal steroids and lower Apgar score were associated with longer LOS
Lee et al. [64]	2016 (2008–2011)	23551	All babies 401 g–1500 g or 22–29 weeks GA plus larger babies meeting specified criteria	Congenital anomalies; death; surgery; readmitted.	USA NICU	Risk models for comparative assessments of LOS need to appropriately account for weight, particularly considering the cutoff of 1,500 g. Refining prediction may benefit counseling of families and health care systems to efficiently allocate resources.
Manktelow et al.[61]	2010 (2005–2007)	4702	23–32 weeks GA	Death; non-normal care.	The UK, Neonatal unit.	Prediction tables permit parents to make sensible estimates about the duration of their baby's stay in the neonatal service; however, there are important differences between units. The variation noted in LOS between otherwise similar units merits further investigation.

Notes: Characteristics of the SR and the included studies on LOS of extremely preterm infants. Table adapted from Seaton et al. 2016

Abbreviations: LOS = lengths of stay; NICU = neonatal intensive care unit; NICHD, SR = systematic review

4.3.2 Findings from literature: Workload and gestational age

For the aspect of workload in relation to GA, no article was identified through the systematic search and only one publication was identified by hand searching. This article by Seaton et al. 2013 was a retrospective, observational cohort study from the UK, describing how changes in survival of EP infants (22+0-25+6) affected the change in workload in NICUs over the past 20 years [66].

zu Arbeitsaufwand in Relation zu GA konnte nur eine Publikation gefunden werden: retrospektive Kohortenstudie (UK)

By use of the two outcome measures, survival and use of respiratory support, Seaton et al. explored an association of increased resource use to survival of EP infants per gestation week. Workload was examined as proportion of required respiratory support (days of ventilation, days of continuous positive airway pressure, CPAP) used in comparison to the total neonatal intensive care population.

Schätzung des Ressourcenaufwands und Arbeitslast anhand des Gebrauchs an Beatmungsunterstützung

The authors showed that infants of 25 weeks or less consume a significant amount of intensive care, measured by the use of respiratory support [66]. The study population accounted for 26.3% of mechanical ventilation and 21.5% of CPAP. The resources allocated to these EP infants increased over time and, concurrently, a significant increase in survival of infants born at 24 and 25 weeks of GA was observed. For infants born at 23 weeks of GA, the authors noted that survival outcomes did not change significantly over the past 20 years, despite the increase in resources.

Resultate können nicht generalisiert werden, und sind auf die spezifische Population limitiert, aufgrund der unterschiedlichen klinischen Vorgehensweisen

Limitations of the study are the lacking generalizability outside the defined population of NICU clinics in the UK due to management differences. Furthermore, due to the retrospective and observational study design, the study results are prone to bias.

4.3.3 Findings from interviews: Lengths of stay and workload in the Austrian context

In the Austrian context, interviewees also stated that EP infants stay longer in NICUs than other preterm infants. The LOS is depending on the GA, whereby an EP infant born at 23 weeks of GA would naturally stay longer and need more care than preterm born at 25 weeks of GA. However, in general, the duration of hospitalization highly depends on the individual patient, since there are very complicated cases of congenital malformations or complicated surgeries for more mature preterm infants that would also necessitate a longer hospital stay.

Krankenhausaufenthalts dauer und GA:

abhängig von GA und individuellen PatientInnen-charakteristika

> *'An infant with 23 weeks will stay until the week 40, so 17 weeks within our unit. So the bed is covered for quite a long time. (...) With 26 weeks it is 3 weeks less.'* (Urlesberger, NICU Graz)

> *'Length of stay is, of course, a problem with regards to hospital capacity. Since most patients are extremely premature infants of 23-25 weeks GA, those patients stay in intensive care for prolonged periods of time which limits capacities for new admissions.'* (Berger, NICU AKH, Vienna)

Interview participants were asked on the relation of GA to the workload of nurses and doctors. The interviewees confirmed that the workload for nurses increases with lower GA of the infants. Apart from GA, however, other factors, such as the case-mix within a department, the applied management approach were related to an increased workload. Limited capacities in terms of workforce and availability of beds would result in transfers from one clinic to another.

Arbeitspensum und GA: Arbeitspensum steigt mit niedrigem GA, aber auch abhängig von Case-mix und Vorgehensweise

Case mix

keine signifikanten Unterschiede in Arbeitslast zw. 23 und 24 GA

Three of the five interviewees argued that while infants with lower GA would make a difference in workload, the difference between infants of the 23 weeks and 24 weeks are not significant.

> *'Of course the younger the patient is, the more staff is needed, because of course there is a difference between a term infant and a very preterm infant. But I think it's not that important. I think the most important thing is to have enough trained nurses to work in neonatal care units. It's not so much the question for me to work with a 23 weeker or a 24 weeker, you need experienced nurses anyway'.* (Kiechl- Kohlendorfer, NICU Innsbruck)

Case-mix: Schweregrad der Fälle und Häufigkeit schwerer Fälle spielt entscheidende Rolle für Arbeitslast an NICUs

Furthermore, the amount of workload is not only influenced by GA of the EP infant, but it is also multiples of higher GAs, patients with congenital malformations, or those in need of dialysis that requires more attention from nurses and doctors. Workload and staff requirements would also largely depend on the degree of severity of cases and the case-mix in a clinic.

> *'Definitely, this [GA] makes a huge difference! (...) but this is also a question of a shortage of beds. Since we are always short of neonatal and paediatric intensive care beds, of course only the very sick and most complicated patients are staying in the wards and all the others that you normally have in other wards, where you have a normal case mix, are transferred. (...) In our neonatal ward with 10 beds, currently, all of the 10 beds are covered with patients with GA 23-25 and most are only 1-3 weeks old. So this is no normal case mix and this makes it complicated (...) and it's not realistic ... that we're going to have less of those extremely premature babies or very complicated babies. It's not only the extremely premature ones, it's also those who need dialysis for instance, so it's not only the gestational week, but it's this case mix – that is very condensed'.* (Berger, NICU AKH, Vienna)

Management

klinische Vorgehensweise:

zB. nicht-invasive Beatmungsmethoden können Arbeitsaufwand beeinflussen

The management approach of a clinic can also influence the workload and the number of nurses needed. In this regard, a less-invasive approach is not necessarily associated with lower workload. On the contrary, if nurses have to actively stimulate patients to achieve the favoured outcomes in survival and morbidity, a higher workload can be expected. Many of the non-invasive approaches lead to significant improvements in outcomes, for example, the less invasive surfactant application (LISA-approach) [67]. LISA, however, requires more staff and time resources than mechanical ventilation.

> *'This is also the basis for our success, the non-invasive approach. We're trying to keep those babies off the ventilator, which sounds less work for the nurses, but the opposite is true! It's a lot more work! (...) Because they have to stimulate them, they have to stay next to the bed and to do non-pharmacological analgesia, position the baby, and constantly work with those patients, which is not so important if this baby is mechanically ventilated, where the baby's stable anyway (...) so lengths of stay is actually not a good marker to capture the work force needs – it also depends on the management approach used'* (Berger, NICU AKH, Vienna)

Transfers

Transfer: Betten- und Pflegekräfteknappheit führt zu Transfers zwischen verschiedenen NICU Kliniken

Several perinatal centres seem to struggle with limited capacities in terms of beds and workforce to respond to an increased needs of intensive care for EP infants. The limited capacity would lead to transfers from one clinic to another if the maximum occupancy rate is reached.

> *'We send our pregnant women to other hospitals because we don't have the capacity to take the babies. And I know it is also the same in Salzburg and in Vienna'.* (Wiesinger-Eidenberger, NICU Linz)

> *'This is the problem that there are not enough intensive care places for neonatal infants in Austria. Vienna often has no further capacity, neither SMZ-Ost nor AKH, and therefore the next phone call is done to Graz. Here in Styria, about 10 high-risk pregnancies are admitted per year from Lower Austria and sometimes from Vienna'.* (Urlesberger, NICU Graz)

The workload decreases with the LOS, i.e. the longer patients stay, the less work they are, since more stable patients and more mature infants (in terms of GA) require less care. Due to the limits in capacity of specialized beds in perinatal centres, some centres need to transfer their patients once they reached a certain maturity or body weight and are stabilized, often resulting in a more dense case-mix of complicated cases with higher workload as stated in the interviews.

The findings from the interviews suggest that, while GA is an important factor when it comes to higher workload and longer LOS in NICUs, it is not the only factor to explain rising resource utilization and resource needs in NICUs in Austria. Other aspects, such as a density of cases requiring highly specialised care, combined with a general shortage of intensive care beds, and a shortage in the workforce would contribute to the increasing resource demands of NICU clinics.

Conclusio aus den Interviews: GA ist wichtiger, jedoch nicht alleiniger Faktor, der Arbeitslast und LOS beeinflusst

4.4 Centre-level factors that influence outcome

Several studies evaluated the potential reasons for international and national differences in terms of mortality and morbidity of EP infants. Variations in patient volume, workload, staffing levels, occupancy rate, intensity of resource use, and different practices regarding care at the limit of viability were some of the factors discussed to influence outcome [38, 68]. These main factors and related studies are summarized in the following chapter outlining different aspects that influence variances in outcomes of EP survival. The study characteristics are presented in Table 4.4-1 in chronologic order.

erhebliche Unterschiede in Überleben und Morbidität Outcomes zwischen verschiedenen Ländern, und Kliniken

potentielle Gründe für Unterschiede:

4.4.1 Findings from literature

Volume-outcome relation

In 2008, a report by the German institute IQWIG was published that analysed the correlation of the number of treated EP infants with the survival outcome [69]. The study found an association between the number of infants treated and mortality rates. In total, 12 publications on 10 studies were identified. Due to their observational study design, no conclusions on causal relationships were drawn. The included studies showed divergent results regarding a statistical correlation between the number of infants treated and their outcomes. For the primary endpoint mortality, the results suggested a significant trend towards a risk-reduction with an increasing volume of EP infants. For secondary the endpoints on morbidity, the scarcity and low quality of data limited the analysis so that no conclusions on the association of the number of treated infants and morbidity were drawn [69].

Volume-Outcome-Relation

Behandlungsqualität und Überlebensraten

In response to this study, and to a policy issued by the German G-BA requiring a minimum annual number of 30 EP infants for tertiary level perinatal centres (level 1 in Germany), the German hospital association (Deutsche Krankenhausgesellschaft) commissioned a study to challenge the findings of the IQWIG report [70]. In a prospective study on a cohort of 7,405 EP infants, they evaluated risk-adjusted mortality rates and hospital differences in terms of annual case numbers [71]. The results showed that, in line with the findings of the IQWIG report, the risk-adjusted mortality rates in small hospitals (annual number of cases <30) are significantly higher than in larger hospitals. Yet, larger hospitals also showed considerable variance in risk-adjusted mortality rates ranging from 3.5% to 28.6%. 56% of EP infants born in larger hospitals had a risk-adjusted mortality rate above average. Among the hospitals that were rated as 'above average' based on risk-adjusted mortality rates, 44% were smaller hospitals with case counts of 14 to 29 EP infants annually. The authors concluded that the annual number of patients is not sufficient to evaluate quality of care, due to the high variance of outcomes even for hospitals with higher case counts. They put an emphasis on the quality-based rather than quantity-based coordination to inform NICU planning, suggesting to take into account centre competences apart from the number of patients [71].

Regionalisation of care

Zentralisierung der Versorgung

Within the EPICure 2 study in the UK, Marlow et al., 2014 evaluated the outcomes of EP infants in relation to place of birth [72]. In a retrospective cohort study of the EPICure 2 cohort, they analyzed whether birth in or transfer to specialized hospitals ('level 3 hospitals' in the UK) would increase mortality and morbidity of EP infants with a GA of 22 to 26 weeks. The study provided the first data to quantify the results of a reorganization in a regionalised structure of neonatal care within the UK, whereby central specialized care centres were created. The findings showed that in 2006, only 56.4% of EP infants were born in the recommended care setting of level 3 services (corresponds to level 1 in Germany, and perinatal care centres in Austria). Birth in level 3 centres was associated with reduced mortality, in particular in hospitals with high activity. In terms of neonatal morbidity, the place of birth and perinatal transfer had little effects on the proportion of morbidities in any setting. The authors suggested that derived from their findings, hospital expertise and case-volume are the main factors influencing outcomes of high-risk pregnancies. Limitations of the study were potential confounders due to differences in case-mix and a lack of information on maternal preferences in terms of place of birth.

Unit size and occupancy rate

Größe der NICU Abteilungen, Auslastung und Ressourcennutzung

A more recent study by Shah et al., 2015 examined the relation between NICU unit size, resource utilization and occupancy rate with the outcomes of preterm infants [68]. They performed a retrospective cohort study of NICUs in Canada. NICU size was defined by the number of beds and categorized in four groups (<16, 16-29, 30-36, >30 beds); occupancy rate was defined as the ratio of the number of admitted infants to the total number of beds. A resource-use-score was computed based on a survey of interventions used per patient. Their findings suggested that infants admitted to larger NICUs (>16 beds) had higher odds for composite adverse outcomes (all-cause mortality, severe morbidities), after adjusting for potential confounders. Furthermore, the results showed that units with higher intensity of resource utilization on the day of admission had higher odds of adverse outcomes. The association of occupancy rates and adverse outcomes showed no significant results. The authors speculated that overuse of resources in NICUs might at times be associated with adverse events and that larger NICUs might be more affected by staff shortage, need for high-intensity care, and lacking care continuum. Limitations of the studies were its observational study design, which limits conclusions on a cause and effect relationship. Furthermore, variations of practices, information on adequacy of staffing, staff competence, and organisational patterns were not taken into account.

Resuscitation decision

Entscheidung für aktives oder passives Vorgehen

Alleman et al., [73] and Rysavy et al., [38] described centre level variances in outcomes within the NICHD network in the US. Based on the data of 16 university hospitals of the Neonatal Research Network (NRN) including 5,418 infants, Alleman et al. modelled centre and individual factors that could account for these differences. The primary outcomes were early mortality (<12 hours after births) and in-hospital mortality. The model took into account differences in selected interventions (provision of antenatal corticosteroids, mode of delivery, mode of ventilatory support etc), their effect on mortality and patient-level differences. Their findings showed considerable variances in the outcomes among the 16 academic hospitals: in-hospital mortality ranged from 11% to 53% for all GAs. Variance was more pronounced for EP infants (<25 weeks) ranging from 28% to 90%. For infants with GA below 25 weeks, centre resuscitation rates significantly predicted mortality. The authors suggested that potential reasons for the benefits of increased interventions for infants below 25 weeks of GA could be the wide range of centres use of supportive therapies. Their findings would indicate that the decision whether to resuscitate very preterm infants affect their mortality.

US-Kontext: Unterschiede in Entscheidung zu aktiven Vorgehen beeinflussen Outcomes

Following-up on these findings, the study by Rysavy et al., analysed if variances in the outcomes are reflected in different hospital practices regarding initiation of either active treatment or comfort care. They analysed data from 24 hospitals included in the NICHD in the US for 4,987 infants born before 27 weeks of GA and limited to infants without congenital malformations. The study showed that the overall rates of active treatment ranged from 22.1% for infants born at 22 weeks of GA to 99.8% for infants born at 26 weeks of GA. The survival rates ranged from 5.1% to 81.4%, for the 22 to 26 weeks of GA, respectively. Hospital rates of active treatment could explain 78% of variation in outcomes among infants born in 22 and 23 weeks of GA, and 22% of the variation for infants born at the 24 weeks GA. However, these findings were limited to infants below 25 weeks of GA. In line with the findings from Alleman et al. [73] intervention rates could not explain variances for infants born at 25 weeks of GA, and hospital variations in active treatment did not account for differences in outcomes for infants born at the 25 or 26 weeks of GA.

ähnliche Ergebnisse für Europa:

For the European context, recent publications presented similar findings to Alleman and Rysavy. Smith et al. and Draper et al. reported data from the EPICE study (Effective Perinatal Care in Europe) comparing care at the limit of viability in Europe [74].

hohe Unterschiede in Überlebensraten für FG der SSW 23 und 24 (23+0-24+6)

Smith et al. studied 1,449 births of EP infants born between 22+0 and 25+6 weeks of GA in five European countries (see Table 4.4-1) [74]. The birth rate of EP infants at 22 to 25 weeks of GA were similar across countries at around 2.8 per 1,000 births. In terms of variability of outcomes, their findings showed a considerable variation in survival to discharge for infants born at 23 or 24 weeks of GA across the different countries. The management and approach to limit of viability seemed to be the influencing factor since countries with higher rates of respiratory support and antenatal steroid provision had higher survival rates. At 25 weeks of GA, the initiation of active treatment was comparable, and, consequently, survival rates did not show significant differences and 52% of infants survived to discharge.

Unterschiede in nationalen und regionalen Richtlinien und Vorgehensweisen dürften ursächlich für die Unterschiede sein

Adding to these findings, Draper et al. 2017 reported on the variability in outcomes after adjusting for population demographics, case-mix, and timing of death [75]. In total, 8,888 infants born between 22+0 to 31+6 weeks of GA were included, from 11 countries and 16 regions in Europe. The overall stillbirth and in-hospital mortality rate was 27.7%, with an almost two-fold difference across regions, ranging from 19.9% in Stockholm to 35.9% in Ile-de France. These variations exist for all outcomes but are most pronounced for early deaths within the first 12 hours after birth. These results suggest that regional policy differences could be the underlying factor for a proportion of this difference, possibly related to the spectrum of interventions for compassionate and palliative care across regions. Adjusting for maternal pregnancy characteristics and infant characteristics, these factors only had a small impact on the variation leaving more than 75% of the variation unexplained. Concluding, the authors indicated that differences in quality of care and variability in management across Europe might account for the majority of the variances in outcomes.

Table 4.4-1: Studies examining centre-level factors that influence outcomes of EP infants

Author	Study Design	Included infants/studies	Objective	Context	Conclusion	Suggested influencing factors
IQWIG, 2008 [69]	SR	10 studies (12 publications)	Association of case number with outcome of EP infants	Germany	Association of case-number with mortality; no conclusions on morbidity, due to low quality of studies	Case volume of EP infants
Kutschmann, 2012 [71]	Prospective Cohort study	7,405 VLBW infants (<1,250g)	Association of case number to risk-adjusted mortality rates	Germany, Baden Würtenberg, 2007-2009; commissioned by DKG	Risk-adjusted mortality rates higher in smaller hospitals with case numbers <30; yet, high degree of variability of results also for larger hospitals; quality-based indicators suggested measure for care planning	Quality of care, and centre competence
Alleman, 2013 [73]	Retrospective cohort study	5,418 VLBW infants, GA 22-28	Factors affecting Center level differences in mortality	USA, NICHD, 2006-2009	High variance in mortality outcomes of academic hospitals in the US (28%-90% for EP infants); centre intervention rates explain proportion of differences in mortality for infants <25 GA;	Center intervention rates
Marlow 2014 [72]	Retrospective Cohort Study 5	2,460 EP infants, GA 22-26,	Effect of balance of birth & perinatal transfer on outcomes	The UK 2006	Higher survival rates in tertiary level hospitals, especially in hospitals with higher activity	Expertise and resources
Rysavy, 2015 [38]	Prospective Cohort study	4,987 infants, < 27 GA	Differences in hospital practices regarding initiation of active treatment and relation to outcomes	USA, NICHD, 2006-2011	Differences in hospital practices regarding initiation of active treatment of EP infants (22-24 GA) explain hospital variation in outcomes	Differences in approach to limit of viability
Shah 2015 [68]	Retrospective Cohort Study	9978 infants, 23-32 GA	Association of NICU characteristics (unit size, occupancy rate, resource utilization)with mortality or morbidity among EP infants	Canadian Neonatal Network, 2010-2012	Larger sized NICUs and higher resource use at the time of admission are associated with higher risk of adverse outcomes	NICU size (>30 beds) resource use on day of admission
Draper 2017 [75]	Prospective cohort study	8888 infants, GA 22-31	proportion of variation in stillbirth and in-hospital of EP mortality rates that persist after adjusting for population demographics, case-mix, and timing of death	16 regions in 11 European Countries (Denmark, Belgium, France Germany, Italy, Netherlands, Poland, Portugal, Sweden Estonia, UK, EPICE birth cohort	Over 4/5th of variation could not be accounted for by maternal, pregnancy, and infant characteristics; inequity in the quality of care provision and treatment of EP infants across Europe likely	Quality of care, differences in management
Smith 2017 [74]	Prospective cohort study	1,449 live births and fetal deaths, GA 22-25+6	International variations in management and survival of EP and VLBW infants	12 regions across Belgium, France Italy, Portugal and the UK, EPICE birth cohort 2011-2012	Percentage of liveborn births was consistently low at 22 weeks and high at 25 weeks but varied internationally at 23 weeks (range 33%–70%) and at 24 weeks (range 5%–71%); antenatal steroids and provision of respiratory support at 22–24 weeks gestation varied between countries	Management and approach to limit of viability/treatment provision

4.4.2 Findings from interviews: Center-level factors in the Austrian context

Österreich spezifische Faktoren, die Outcomes beeinflussen laut Interviews:

Interview participants were asked to provide factors that have an influence on the outcome of EP infants in the Austrian context. The experts agreed on the importance of centre competence, and the number and frequency of patients (occupancy). Further prognostic factors would be the number of available, trained staff, in particular nurses, the quality of antenatal transportation, and quality and equipment in NICUs.

Case count and expertise

Expertise und Kompetenz der Zentren

Survival as well as morbidity, and neurological impairment would be significantly improved in larger hospitals with a higher case count and a high level of expertise.

Fallzahl

> *'You must treat a lot of patients to have an idea what you should do ... it is not the routine of the doctors but the routine of the nurses ..."*
> (Wald, NICU Salzburg)

> *'Expertise comes with volume. So it's both, volume and the expertise. It has been shown that the best outcome is within units that have more than 100 or around 100 infants below 1,500 grammes a year. So, I think there is no question, absolutely no scientific question, that centralisation [i.e. regionalisation] is the thing to improve outcome.'* (Urlesberger, NICU Graz)

Centralisation/Regionalisation

Zentralisierung der Versorgung

One way to establish expertise and quality of care is achieved by the centralisation of services, also referred to as regionalisation[5], and different levels of care provision. In Austria, seven perinatal care centres provide the whole range of intensive care and treatment, responsible for care at the limit of viability at 23 and 24 weeks of GA. The next level of care provision takes places in type A centres (Schwerpunktzentrum Typ A) that provide care from 25 weeks of GA onwards, as determined by the ÖSG (Österreichischer Strukturplan Gesundheit) [59].

> *'Yes, it (a centralised/regionalised system) is the best way to organise it, it's the only way to improve outcome. This has been proven in many studies, and this is the way I think it will work in future. (...) We have a very disciplined group of external hospitals and we do have only preterm infants below 1500 grams once or twice a year outside of Graz.'* (Urlesberger, NICU Graz)

While the regionalisation into perinatal centres and type A centres is working well, which is also confirmed by data from the Austrian birth registry [77] some interviewees mentioned immanent problems with guaranteeing hospital capacities for EP infants leading to a transfer of pregnant women from one hospital to another. Also, the necessity to transfer EP infants to another hospital once they reached a certain age and are stabilized is not an optimum, since this could potentially influence outcomes as a result of a reduced continuum of care.

[5] The term regionalisation refers to the recommendation that infants with very low birth weight should be born at highly specialized hospitals, most commonly designated as level III hospitals [76].

Training of workforce and team coherence

The training of nurses and doctors and the importance of teamwork and team excellence were also mentioned as influencing factors.

Training und Zusammenhalt im Team

> *'We realized it really needs a lot of training, expertise, and many efforts in the team. It's no use starting with 23 weekers if you're caring for 1 to 5 of those babies per year. You really need to centralize this in very few, highly specialized centres.'* (Berger, NICU AKH, Vienna)

Differences in approach to care at the limit of viability

One factor that is not likely to affect the differences in outcomes of EP infants in Austria are different approach to care at limit of viability as suggested by Rysavy et al. and Alleman et al. for the US [38, 73]. In line with the Austrian recommendation on the care at the limit of viability [14], the heads of NICUs confirmed that perinatal care centres in Austria start resuscitation at 23+0 weeks of GA, through a shared-decision making process with the parents of the child. Adhering to these guidelines, NICUs in Austria provide comfort care for infants born before 23+0 weeks of GA (22+0-22+6). Only in very rare instances, when, for example, there is no knowledge on the exact GA, or the accuracy of the GA estimate is questioned, these infants would receive active life support.

kein Einfluss auf Unterschiede in Outcomes: Entscheidung zw aktivem und passivem Vorgehen

da Vorgehen laut Konsensusleitlinie

> *'... We do not resuscitate 22 weeks babies, they would receive palliative care. Only in very rare instances and very special occasions, we would probably decide to actively care for a 22 weeker. In general, these babies are not actively resuscitated in our institution and in whole Austria. (...) Maybe in 10 years, we will also go for the 22 weekers, but I do not see it right now because we still have problems with the 23 weekers. Although, the outcomes are really good compared to 5 or 10 years ago.'* (Berger, NICU AKH, Vienna)

aktive Behandlung in der 22 SSW nur in Ausnahmefällen

Management

In accordance with the findings by Smith et al. and Draper et al., differences in management approaches were also mentioned by the interviewees to influence outcomes on the national level [74, 75]. While NICUs in Austria have a similar approach to care at the limit of viability, the management and treatment approaches differ in the centres. For instance, the perinatal centre of the AKH, Vienna, has gained excellences and competences with the afore-described non-invasive 'LISA' approach (Less Invasive Surfactant Administration)[67]. Since initial evidence has shown substantial improvements in outcome, this approach is also employed in some other NICUs in Austria, such as in Salzburg and Innsbruck. Since experience with a certain approach was mentioned as a pivotal factor to improve outcomes, other perinatal centres prefer using established techniques where they have more experience. Also, the available support programs differ in the different centres. For instance, the NICU in Salzburg established the first NIDCAP (Newborn Individualized Developmental Care and Assessment Program) centre in Austria, which provides a comprehensive support program to improve neurodevelopmental outcomes.

allerdings: Unterschiede in klinischem Management durch unterschiedliche Interventionen und Therapieoptionen

If centre-level differences in outcomes exist could not be established through the interviews. Factors that could potentially influence hospital variations in outcomes in Austria are different levels of expertise, case-volume, and resource capacities in terms of workforce. Furthermore, differences in treatment approaches could influence variations in outcomes. However, one factor that seems less relevant for the Austrian context are differences in the approach to care at the limit of viability.

unklar ob und wie hoch Unterschiede in den klinischen Outcomes zw. verschiedenen Perinatalzentren neue Konsensusleitlinie seit 2017

Overall, outcomes of preterm infants have substantially improved over the past decades in Austria, which is also reflected in the update of the common guidance document on care at the limit of viability [14]. In comparison to the former version, the limit of viability is now set at 23 to 24 weeks, instead of 23 to 25 weeks, as a result of the promising outcomes in terms of survival without impairment achieved for infants born at 25 weeks of GA.

5 Discussion

This report outlined the current evidence on outcomes of extremely preterm births at the limit of viability and the consequences for resource use and needs. We aimed to provide a comprehensive overview of these two complex aspects of prematurity at the limit of viability. We here discuss findings and related considerations for health care planning purposes.

Evidenzübersicht zu Outcomes und zu Ressourcennutzung

Level and quality of evidence on outcomes

A vast number of cohort studies exist assessing the outcomes of EP infants in terms of survival and/or survival with or without impairment. These studies stem from various regions of the world and provide data from large, international neonatology networks, such as the VON network, the iNEO [78], or the US-based NICHD network [38]. Given this large amount of primary studies, it was surprising that only few systematic reviews (SR) on survival or on neurodevelopmental outcomes were found for the purpose of this review.

große Anzahl an Primärstudien vorhanden

aber nur wenige systematische Übersichtsarbeiten

We could identify only four SRs that addressed survival of EP infants, of which one was limited to the US context and two were of poor quality. There were only two SRs that evaluated neurodevelopmental outcomes, yet, using different endpoints and follow-up periods.

nur 4 SR zu Überleben und 2 SRs zu NDI

One very recent SR was identified during the initial scoping phase. This study was conducted by the Norwegian Institute of Public Health addressed both outcomes of interest, yet, it was written in Norwegian language and thus needed to be translated into English. Due to the recent publication date of March 2017, and the good AMSTAR rating of 10 of 11, we refrained from updating the search, but we re-evaluated the quality of evidence according to the GRADE scheme. Additionally, one SR on long-term neurodevelopmental outcomes was considered for the results on neurodevelopmental outcomes of extreme prematurity.

1 SR aus 2017 zu Überleben und NDI, allerdings in norwegischer Sprache

zusätzlich 1 SR zu Langzeitsoutcomes für NDI

Results from systematic reviews on survival

The MA by Myrhaug et al. showed that the survival of infants born at the limit of viability ranged from 9% for infants born at 22 weeks of GA, 27% at 23 weeks, 55% at 24 weeks and 73% for infants born at 25 weeks (survival rates were calculated as percentage of liveborn infants) [1]. When calculating survival rates as percentage of infants transferred to NICUs, the survival rates were considerably higher with 33%, 48%, and 68% for 22, 23 and 24 weeks of GA, yet remain similar for the 25 weeks of GA with 75%.

Überleben (als % der Lebendgeborenen und % der Transfers in NICUs):
22 SSW: 9 % und 33 %
23 SSW: 27 % und 48 %
24 SSW: 55 % und 68 %
25 SSW: 73 % und 75 %

The results of the MA were very heterogeneous, in particular for the 22 and 23 weeks of GA, and, subsequently, the quality of evidence was rated very low.

Qualität der Evidenz sehr niedrig aufgrund hoher Heterogenität der Ergebnisse;

The finding that the two denominators 'liveborn infants' and 'infants transferred to NICUs' produce considerably different results in terms of survival rates for births at the limit of viability (22-24 weeks of GA) underlines the argumentation that the choice of denominators can lead to bias when reporting survival rates [37]. Survival rates solely based on infants transferred to NICUs are likely to overestimate survival as the number of non-survivors before transfer is not taken into account [36]. Yet, on the other hand, several authors argued that an adequate interpretation of survival rates is only possible if the context whether resuscitation was attempted is considered [6, 14, 79].

große Unterschiede zw. den MAs der zwei Denominatoren (% der Lebendgeborenen und % der NICU-Transfers)

Entscheidung zu aktivem oder passive Vorgehen kann Einfluss auf Outcome haben

In this regard, the initial management of active or comfort care has a considerable impact on the predicted survival of infants at the limit of viability as shown in studies by the NICHD network and studies from Sweden by Serenius et al. [38, 80]. Data from the NICHD network reported that survival estimates change as much as 20% if survival is calculated only for infants that received active treatment. Serenius et al. demonstrated that a proactive perinatal care decreases mortality without increasing the risk of neurodevelopmental impairment at 2.5 years corrected age for infants below 27 weeks of GA [80].

Ergebnis unterstreicht Wichtigkeit der Auswahl einheitlicher Denominatoren bei Vergleich von Überlebensraten

For research and policy, this finding highlights the importance of using identical denominators when comparing results from different cohort studies. Studies reporting more than one denominator are more useful to compare outcomes, since based on these estimates, a conclusion on the impact of active treatment on survival of EP infants is possible and potential over- or underestimation are avoided.

Variations in outcomes data

große Unterschiede zw. den Ergebnissen einzelner internationaler Studien, und österreichischen Ergebnissen

Comparing the results of the MA with the results from large cohort studies and the results from the Austrian preterm-birth register, the considerable variation in outcomes between study cohorts, regions, and hospitals becomes visible (see Figure 3.1-2). While, for instance Sweden and Austria had the highest survival rates for infants born at 23 or 24 weeks of GA, with around 50% (23 weeks) and around 70% (24 weeks) of infants surviving, the outcomes of the Epipage study conducted in France showed few survivors in 23 weeks of GA and only 30% at the 24 weeks of GA [27].

Gründe könnten in Unterschieden in Expertise, Fallzahl, Ressourcenkapazitäten, Therapieoptionen und Qualität der Versorgung liegen

Several reasons for these differences were discussed in the literature and are outlined in chapter 4.4. These factors explain in country variabilities, such as the level of expertise, case volume, different resource capacities, but also varying treatment options and quality of care [74]. Differences in between international cohorts were related to the quality of care and the varying approaches to care at the limit of viability [38]. The latter is discussed in the second part of this project[16], comparing differences in international guidelines on the limit of viability (chapter 3). In the US, for instance, these differences in the approach to the limit of viability seems to be the key factor to explain hospital variability in outcomes [38].

für den US Kontext wurden Unterschiede in aktivem und passivem Vorgehen als Hauptursache gefunden

In Austria, different approaches to the limit of viability seem to play a minor role. In five interviews with the heads of NICUs, interviewees empathized the recent Austrian consensus guideline issued in 2017, whereby all perinatal care centres in Austria start considering active treatment at 23 weeks of GA, through a shared-decision making process with parents [14].

dies scheint in Österreich untergeordnete Rolle zu spielen, wobei unklar ist ob Unterschiede bestehen

If differences in survival and morbidity rates of EP infants exist in Austria and how pronounced such differences between perinatal care centres are, could not be determined in this report due to lacking literature and access to data on the outcomes for each perinatal care centre in Austria.

Deutschland: hat zu diesem Zweck Monitoring Prozess an allen Perinatalzentren geschaffen

In Germany, in response to a broad policy debate around quality of care at the limit of viability and differences in survival outcomes of different hospitals [71], the G-BA commissioned a monitoring process of perinatal care centres including a public website to monitor survival outcomes of individual perinatal centres (level I and II) and to facilitate national comparison [81]. This website, which is managed by the IQTIG (Institut für Qualitätssicherung und Transparenz im Gesundheitswesen) is targeting parents and non-experts and provides them with outcome data of all specialised perinatal centres in Germany.

Results from systematic reviews on neurodevelopmental impairment

Results from the SR by Myrhaug et al. showed that the chances for survival without severe impairment were estimated to be 43%, 47%, and 61% at 23, 24, and 25 weeks of GA, respectively. For infants born at 22 weeks of GA, data was too limited to conclude on the chances of survival without impairment.

Überleben ohne schwere Beeinträchtigung:
23 SSW: 43 %
24 SSW: 47 %
25 SSW: 61 %

In comparison to the data on survival, the quality of data on NDI was poor, with a limited number of data and studies per GA. The quality of evidence was graded to be very low for the GAs 22-25.

Qualität der Evidenz für NDI sehr niedrig

Furthermore, long-term data to assess NDI was scarce. We identified one additional SR by Moore et al. including nine studies that evaluated NDI at four to eight years. The study showed that 60%, 70%, and 75% of infants born in 23, 24, and 25 weeks, respectively, have a chance of survival without moderate or severe impairment. For 22 weeks of GA, data was only available for 12 infants, and thus, no conclusions on long-term risk of NDI could be drawn from the results. Furthermore, due to lacking information on the RoB of the included studies, we could not evaluate the quality of evidence with GRADE.

wenige Langzeitdaten: 60 %, 70 % und 75 % (SSW 23, 24,25) der FG überleben ohne moderate oder schwere Einschränkung

The risk of NDI is more challenging to assess than survival rates. EP infants who survive initial hospitalization follow a wide spectrum of different NDI outcomes. A whole range of different outcomes needs to be evaluated to provide a holistic and comprehensive picture of the risk of impairment, ranging from cerebral palsy to impaired vision, and hearing. Furthermore, these outcomes are measured with different scales and tools, limiting international comparison of the results. Moreover, socioeconomic factors are often not taken into account although markedly influencing the long term outcome of very preterm infants [44].

NDI-Risiko: keine einheitlichen Definitionen und verschiedene Einflussfaktoren erschweren Vergleich und Analyse

For the purpose of this review, we focused on NDI measured with the Bayley scales, which represents the most commonly applied tool for the assessment of NDI [4]. However, this measurement has limitations since studies suggested that the Bayley II score may potentially overestimate adverse neurological outcomes, while the current edition of the Bayley Scale, Bayley III, may underestimate NDI at two years of age. Results were therefore presented for each scale individually, however, limiting the validity of the results due to a smaller sample size.

inkonsistente Resultate inwiefern sich NDI mit Behandlungsfortschritte n verbessert hat;

Studies on neurodevelopmental outcomes provide inconsistent results whether the risk of impairment has improved along with survival advances in perinatal care [13]. The improved rates of survival in EP births have not been sufficiently matched to conclusive evidence on a reduction in rates of NDI [82], due to the limited comparability of studies and differences in practice over time. Consequently, NDI outcome data on a national level, and in particular long-term data for EP survivors, would be needed to evaluate improvements in terms of neurodevelopmental outcomes for Austria.

Langzeitdaten und nationale Daten zur Evaluierung nötig

Implications of extreme prematurity in the Austrian context

Data and research on periviable birth in Austria are scarce. We could identify only few publications that were relevant for the scope of this report, even after having asked the interviewed experts to provide additional literature. Since 2013, an Austrian register for outcomes of preterm infants has been set in place, the 'Frühgeborenen Outcome Register', which is hosted by the GÖG (Gesundheit Österreich GmbH). The register allows NICU clinics to enter their outcome data on a voluntary basis. Today, the register consists of outcome data of an estimated 85% of preterm births in Austria. However, so far no publications on the results of this register were available.

Frühgeborenen Outcome Register

Daten zur Anzahl der EFG von Statistik Austria: 2016: 6675 FG (7,7 %), davon 350 EFG (5,2 %)

Data on the current number of preterm infants per gestation week are available from Statistik Austria [2]. The trend of the past 20 years showed a present reduction in the percentage of preterm births in relation to liveborn infants in Austria, with a slight decrease in numbers since 2008. The number of EP infants remained relatively steady over the past years, with a slight increase in the past two years, and 350 EP infants in 2016. Conversely, no Austria specific publications on the survival outcomes or long-term outcomes of EP infants were available. The outcome data retrieved for the purpose of this report stemmed from the recent Austrian guideline, however, are limited to 23 and 24 weeks of GA [14].

aufgrund fehlender Österreich spezifischer Literatur: Interviews mit 5 Perinatalzentren

Interviews: verbesserte Outcomes führen zur Erhöhung des Ressourcenbedarfs; Pflegefachkräftemangel spielt national wie international eine entscheidende Rolle

Due to the scarcity of data for the Austrian context, interviews with five heads of perinatal care centres in Austria were conducted to gather data on the resource implications of periviable birth. The interviewees highlighted that there is a trend towards improved outcomes of EP infants, not only in terms of survival, but also in survival without or with only mild impairment. This positive trend, however, is accompanied by an escalation of resource utilization and workload, due to the complex patient-case mix. Furthermore, the use of novel, non-invasive treatment approaches increases the necessity of trained workforce. In line with international literature, ensuring an adequate level of nurse staff to respond to the increased workload was identified as key challenge shared amongst NICU clinics in Austria. The current shortage of nurse staff could not only lead to a deterioration of outcomes for patients, but also to closed beds and transfers from one clinic- or even one region to another.

Limitations

Limitationen: Analyse der Outcomes auf Sekundärstudien beschränkt

There are several limitations to this report. First, we limited the analysis on outcomes of secondary research evidence, i.e. SRs, MAs. These inclusion criteria were decided based on the scoping analysis that identified a vast amount of primary studies and a recent high-quality SR (although in Norwegian). These scoping results not only indicated that there would be several SRs on the topic, but also rendered a re-analysis of the Norwegian MA redundant. However, to highlight the differences in between primary studies, we considered selected cohort studies stemming from different regions to show variability in outcomes and the challenges in interpreting these data.

daher nur eingeschränkte Möglichkeit das Bias-Risiko zu bewerten

The limitation to secondary research for the sake of analysis also limited the possibilities to assess RoB. We re-evaluated the quality of evidence for one SR, where RoB was reported for each study. However, this was not the case for the SR of long-term neurodevelopmental outcomes and thus we could not perform GRADE for this outcome.

Ressourcennutzung: breite Suche und Suchbegriffe

In chapter 3 of this report, we aimed to provide an overview of the available evidence and outline the different aspects associated with resource scarcity and care for EP births. We performed a systematic search combined with a thorough hand search, by screening the reference list of included studies. However, due to the broad concepts of resource needs and the vast amount of publications on periviable birth, it could be that further relevant publications were missed. Yet, we believe that the included studies provide a solid basis to shape an understanding of resource requirements in NICUs to inform care planning.

As aforementioned, there is scarcity of literature-based data on EP infants from the Austrian context. Consequently, in addition to evidence from literature, we interviewed the heads of five perinatal care centres in Austria to gather context-specific data. While a diversity of interview participants would have been even more favourable, for example by also interviewing nurses, we were limited in time resources and thus decided to focus on one key stakeholder, yet to account for regional differences in Austria.

Interviews: nur mit Klinikleitung ohne maximale Diversität der Interview TeilnehmerInnen

6 Conclusion

The findings of this suggest that despite the large amount of publications on the topic of prematurity, systematically reviewed evidence is scarce. While several international cohort studies exist, this is not reflected in the number of SRs.

trotz Vielzahl an Publikationen zum Thema Frühgeburtlichkeit, nur wenig systematische Literatur zu Outcomes, ins besondere Langzeitstudien zu NDI

We noticed that – apart from the general lack of SRs in the field with a high research output – there seems to be a paucity of long-term outcome data that are systematically assessed. As a follow-up for this research, we would thus propose a SR of long-term outcomes to get a more precise picture of research on long-term outcomes of EP survivors.

empfohlene Schritte: Datenerhebung und Analyse österreichischer Daten zu Outcomes und Ressourcennutzung

In order to capture resource needs for the Austrian context, the next step would need to be to analyse primary quantitative data. Data as such, e.g. on outcomes, LOS, and interventions, would allow planning of resource allocation and cost-budget as well as impact analysis.

einheitliche Monitoring- und Evaluierungsprozesse für Perinatalzentren

Regarding quality of care management for the care of periviable infants, outcome data of different Austrian clinics would give insights into potential centre level differences in outcomes. The example of Germany to monitor quality of care in a transparent manner and making it accessible to non-experts and researchers provides an idea of how the future quality management of periviable birth could look like.

7 Literature

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8 Appendix

8.1 Quality appraisal with AMSTAR

Table 8.1-1: AMSTAR score for each of the identified systematic reviews

First author, year [reference]	Type of SR	AMSTAR assessments											
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Bellieni et al. [83]	SR	✓	-	no	no	no	no	no	-	no	no	no	1
Ishii, et al. [84]	SR	✓	-	✓	no	no	no	no	no	no	no	✓	3
Hamisu, et al. 2013 [85]	SR, MA	✓	✓	✓	-	no	✓	✓	✓	✓	✓	✓	9
Moore et al., 2013 [18]	SR, MA	✓	✓	✓	✓	no	✓	no	✓	✓	no	✓	8
Myrhaug et al.2017 [1]	SR, MA	✓	✓	✓	✓	✓	✓	✓	✓	✓	no	✓	10

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Figure 8.1-1: AMSTAR tool to assess the quality of systematic reviews, by Shea et al, 2009

Table 8.1-2: Data Extraction table of systematic reviews on survival and neurodevelopmental outcomes

Author, year	Study type	Aim of the study	Intervention/Exposure vs Comparison	Main endpoints	Inclusion criteria/Exclusion criteria	Period searched	AMSTAR
Bellieni et al, 2012 [83]	SR	Review most recent data on outcomes of very premature babies (22-25 weeks GA)	Exposure: being born extremly premature < 26 week GA Comparison none	❂ Survival rates ❂ Long-term outcome (not specified)	❂ English ❂ Data on health or survival of preterm infants < 26 GA ❂ Data on survival rates or neurodevelopmental outcomes of very preterm infants ❂ Data presented per gesational week	January 2010–May 2012	
Ishii et al, 2013 [84]	SR and cohort study	To provide insturctive information on death, neurodevelopmental, out-comes of infants born at 22 and 23 weeks' gestational age	Exposure: being born extremly premature in week 22 and 23 GA Comparison none	Survival Neurodevelopmental impariment defined as cerebral palsy, hearing impairment, visual impairment, and a developmental quotient, 70.	❂ English ❂ Outcomes of infnats born during or after 1990, ❂ cases of death and NDI at 18 to 42 months for infants born < 28 weeks GA	January 2000–June 2012	
Hamisu et al. 2013 [85]	SR, MA	To review observational studies that adress the survival of previable gestation in the US	Exposure: Being born <24 GA/ and or <500g Comparison none	Survival >24 h up to 1 year: survival at discharge and survival beyond post-natal period (up to 1 year)	❂ Cohort studies ❂ Population: EP infants < 24 GA, born in the US ❂ Published between January 2003–January 2013 ❂ Exclusion studies did not assess survival, or if no denominator wasnot know,	Published between 2003–2013	
Moore et al., 2013	SR, MA	To determine the rate of moderate to severe and severe NDI by GA in EP followed-up between 4 to 8 years	Exposure: beeing born extremly premature (22-25 GA) Comparison: term infants	❂ Moderate NDI: IQ score 2- 3 SDs below the mean, ambulant CP (GMFCS: 2-3), little useful vision, or hearing restored with amplification ❂ Severe NDI: IQ score >3 SDs below the mean, non-ambulant CP (GMFCS: 4-5), no useful vision, or no useful hearing de-spite hearing amplification	❂ Population: Extremely preterm infants born with a GA of 22-25 at the age of 4-8 years ❂ Data from high income countries ❂ Studies: prospective cohort studies, follow-up rate > 65%, use of standardised testing for NDI	2004–2013	
Myrhaug et al. 2017 [1]	SR, MA	To evaulate the prognosis for extremely premature infants who have undergone acute life-saving treatment for a) survival and b) morbidity from discharge	Exposure: being born extremly premature Comparison none	❂ Primary outcomes:survival at discharge, at one to ten years (see above) ❂ Secondary outcomes: Cerebral Palsy, autism, ADHD, impaired vision, Lung problems, school performance, and/or other health-related outcome from discharge to Home for cohorts and with ≥5 yrs follow-up time for randomized Controlled studies	❂ Population: Extremely preterm infants born with a GA of 22-27. ❂ Context: high income countries, children born from 1998 until 2015 ❂ Study-design: SR of cohort studies; SR of of RCTs, Cohort studies (as of 2000) ❂ Language: English, German, French, Norwegian, Swedish and Danish	2000–June 2015	10

8.2 Interview material

INTERVIEW GUIDE

Objective of the study

Against the backdrop of medical advances in neonatal intensive care and the increased survival rate of infants at the limit of viability, the aim of this project is to assess resource planning, outcomes, and ethics of children born extremely prematurely in neonatal intensive care units (NICUs) in Austria.

In the first part, we aim to provide evidence on the clinical outcomes of extremely preterm infants as well as data into the resources needed at NICUs to care for these infants. In the second part, we aim to provide information on "good practice" models of decision-making procedures (choosing between active vs palliative treatments), the social factors that serve as the basis for making the decision whether to prolong life (parents' age, educational background, or socio-economic status), and the ethical challenges with interventions at the threshold of viability.

Information on the interview:

The interview will take approximately 30 minutes. The interview will be recorded, transcribed and a copy of it will be sent back to you to confirm the content. Personal information provided during the interview will be kept confidential. The following questions will be the main topics that will guide the interview:

Guiding Questions for semi-structured interviews:

Part I: Resource Needs NICU for preterm infants:

1. **Where are current short comings and resource needs in NICUs?**
   - Does your clinic have staffing requirements? Are staffing requirements feasible?
   - What is the doctor per patient and nurse per patient ratio on average?
   - Do you need more health personnel (doctors/nurses) depending on the gestation week of your patients?
   - Institutional guidelines, differences in management guidelines
2. **workload and resource needs by gestation week:**
   - Average lengths of stay/differences of LOS in relation to in gestation weeks
   - differences in resource needs/use by gestation week
   - differences in nurse-to patient ratio
3. **center level factors that influence outcome**
   - What are the center level factors that influence outcome? (level of specialization, management, number of nurses available, volume of preterm infants/year, difference in approach to active/or palliative care)

Part II: Ethics

- How do the guideline criteria for deciding between active and palliative treatment translate into reality?
- Do you have any standard operating procedures (SOPs on process how to invite the parents, who leads the discussion, predefined questions) specific for your institution?
- How do social factors like educational or socio-economic background of parents influence the decision-making process?
- What are the key ethical struggles in your experience? What do you think are the key qualities (excellences of character or virtues) of the profession of decision-making in NICU?

Table 8.2-1: Code tree

Overall Theme	Code	Subcode	Coding example
Health personnel and workforce	Nurses	Nurse-to-patient ratio	*'We have to be very careful if we talk about ratios. You know, ratios, do you mean intensive care places versus nurses? Or do you mean a 1:1 nurse situation in high-risk patients. So this is getting mixed up very often. So, for each of the local intensive care place there are 2.5 nurses, but we can switch to 1:1 nursing on demand.*
		Nurse training	*'The problem is definitely that there are not enough nurses trained. (…) From 2013 onwards, we had 60 young pupils starting training every year until 2016. We had 2 cohorts of 60 nurses who started, so it was like 50 or 52 who finished. And still, we didn't have enough because we were always increasing our beds and other hospitals too'*
		Nurse shortage	*'Since I have been working here, we always had a lack of nurses! We always had beds closed although it was always a shortage of beds, yet we always had some that were closed because we did not have enough nurses.'*
	Medical doctors	Workforce	*'We all lost a lot of … let's say time of medical doctors within the work. This was not compensated with increase in numbers of medical doctors, and we lost 20% of our doctoral power'*
Hospital capacity	Context	Number of beds	*'We have 12 intensive care bed and six intermediate care beds at the moment 2 of the intensive care beds are closed and 2 intermediate care beds, because we do not have enough nurses'*
		Transfer	*'We send our pregnant women to other hospitals because we don't have the capacity to take the babies. And I know it is also the same in Salzburg and in Vienna!'*
		GA and LOS	*'Staying longer is not a problem because a 23 weeker with a chronological age of 6 or 7 or 8 weeks is a lot less work for the nurses than a 23 weeker or 24 weeker or 25 weeker in the first week of life for instance'*
	Lengths of stay	Case-mix	*'It's not realistic … that we're going to have less of those extremely premature babies or very complicated babies. It's not only the extremely premature ones, it's also those who need dialysis for instance. We are the only hospital in whole of Austria who is doing renal replacement therapy in premature babies, very very laborious for nurses, so it's not only the gestational week, but it-it's this case mix- that is very condensed'*
	Workload	GA and workload	*'… This is not entirely correct, because, in the week between 23 and 24, we stop the treatment earlier, so if there is a worse outcome, we stop the treatment. So of the 23 weekers, there are not many bad- outcome patient alive. In the 24/25 weekers, there are more patients alive with a bad outcome, because we cannot stop the treatment so easily. So that's a-a little bit a problem so because if the gestational age is lower, the outcome is not so good. There are only 3 weeks with bad outcomes: 23,24,25. Up to 26 weeks there is no real difference and up to 27 weeks no patient dies.'*
Center-level factors	Care at limit of viability		*'… We do not resuscitate 22 weeks babies, they would receive palliative care. Only in very rare instances and very special occasions, we would probably decide to actively care for a 22 weeker. In general, these babies are not actively resuscitated in our institution and in whole Austria. (…) Maybe in 10 years, we will also go for the 22 weekers, but I do not see it right now because we still have problems with the 23 weekers. Although, the outcomes are really good compared to 5 or 10 years ago.'*
	Centralization/ Regionalization		*'Yes, it (a centralized/a regionalized system) is the best way to organise it, it's the only way to improve outcome. This has been proven in many studies, and this is the way I think it will work in future. (…) We now have a very disciplined group of external hospitals and we do have only preterm infants below 1500 grams once or twice a year outside of Graz. '*
	Expertise		*'You must treat a lot of patients to have an idea what you should do….it is not the routine of the doctors but the routine of the nurses …'*
	Case-count/ Volume		*'Expertise comes with volume. So it's both, volume and the expertise. It has been shown that the best outcome is within units that have more than 100 or around 100 infants below 1500 grams a year. So, I think there is no question, absolutely no scientific question that centralisation is the thing to improve outcome.'*
	Interventions/ Managment	LISA	*'This is also the basis for our success, the non-invasive approach. We're trying to keep those babies off the ventilator, which sounds less work for the nurses, but the opposite is true! It's a lot more work! (…) Because they have to stimulate them, they have to stay next to the bed and to do non-pharmacological analgesia, position the baby, and constantly work with those patients, which is not so important if this baby is mechanically ventilated, where the baby's stable anyway. (…) so lengths of stay is actually not a good marker to capture the workforce needs- it also depends on the management approach used'*

8.3 Literature search strategies

8.3.1 Outcomes

Chochrane

Search Name: Outcomes of Extremely Preterm Birth (KH/MS)	
Search Date: 14/06/2017	
ID	Search
#1	MeSH descriptor: [Infant, Extremely Premature] explode all trees
#2	((extreme* or very) near ((prematur* or preterm or early) near (newborn* or neonate* or baby or babies or toddler* or infant* or child* or birth* or deliver*))):ti,ab,kw (Word variations have been searched)
#3	periviable birth*:ti,ab,kw (Word variations have been searched)
#4	#1 or #2 or #3
#5	MeSH descriptor: [Fetal Viability] explode all trees
#6	Periviability:ti,ab,kw (Word variations have been searched)
#7	Limit* near viability:ti,ab,kw (Word variations have been searched)
#8	MeSH descriptor: [Survival] explode all trees
#9	MeSH descriptor: [Survival Rate] explode all trees
#10	surviv*:ti,ab,kw (Word variations have been searched)
#11	MeSH descriptor: [Pregnancy Outcome] explode all trees
#12	MeSH descriptor: [Treatment Outcome] explode all trees
#13	outcome parameter*:ti,ab,kw (Word variations have been searched)
#14	outcome*:ti,ab,kw (Word variations have been searched)
#15	MeSH descriptor: [Outcome Assessment (Health Care)] explode all trees
#16	MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees
#17	neonatal intensive care unit*:ti,ab,kw (Word variations have been searched)
#18	NICU:ti,ab,kw (Word variations have been searched)
#19	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20	#4 and #19 Publication Year from 2013 to 2017, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Methods Studies, Technology Assessments and Economic Evaluations

Total: 66 Hits

CRD

Search Name: Outcomes of Extremely Preterm Birth (KH/MS)	
Search Date: 14/06/2017	
ID	Search
1	MeSH DESCRIPTOR Infant, Extremely Premature EXPLODE ALL TREES
2	(((extremely or very) NEAR ((prematur* or preterm or early) NEAR (newborn* or neonate* or baby or babies or toddler* or infant* or child* or birth* or deliver*))))
3	(peri*viable birth*)
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR Fetal Viability EXPLODE ALL TREES
6	(Peri*viability)
7	MeSH DESCRIPTOR Survival EXPLODE ALL TREES
8	MeSH DESCRIPTOR Survival Rate EXPLODE ALL TREES
9	(surviv*)
10	MeSH DESCRIPTOR Pregnancy Outcome EXPLODE ALL TREES

11	(outcome parameter*)
12	(outcome*)
13	MeSH DESCRIPTOR Treatment Outcome EXPLODE ALL TREES
14	MeSH DESCRIPTOR Outcome Assessment (Health Care) EXPLODE ALL TREES
15	MeSH DESCRIPTOR Intensive Care Units, Neonatal EXPLODE ALL TREES
16	(neonatal intensive care unit*)
17	(NICU)
18	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	#4 AND #18
20	* FROM 2013 TO 2017
21	* WHERE LPD FROM 01/01/2013 TO 13/06/2017
22	#20 OR #21
23	#19 AND #22

Total: 27 Hits

Embase

Search Name: Outcomes of Extremely Preterm Birth (KH/MS)		
Search Date: 14/06/2017		
No.	Query Results	Results
#46	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR ‘periviable birth*’ AND (‘fetal well being’/exp OR peri*viability OR ‘newborn mortality’/exp OR ‘survival rate’/exp OR ‘survival’/exp OR surviv*:ti,ab OR ‘clinical outcome’/exp OR ‘pregnancy outcome’/exp OR ‘outcome parameter*’ OR ‘fetus outcome’/exp OR ‘outcome assessment’/exp OR ‘treatment outcome’/exp OR outcome*:ti,ab OR ‘neonatal intensive care unit’/exp OR ‘neonatal intensive care unit*’:ti,ab OR nicu:ti,ab) AND (‘meta analysis’/de OR ‘systematic review’/de) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR ‘periviable birth*’ AND (‘fetal well being’/exp OR peri*viability OR ‘newborn mortality’/exp OR ‘survival rate’/exp OR ‘survival’/exp OR surviv*:ti,ab OR ‘clinical outcome’/exp OR ‘pregnancy outcome’/exp OR ‘outcome parameter*’ OR ‘fetus outcome’/exp OR ‘outcome assessment’/exp OR ‘treatment outcome’/exp OR outcome*:ti,ab OR ‘neonatal intensive care unit’/exp OR ‘neonatal intensive care unit*’:ti,ab OR nicu:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR ‘periviable birth*’ AND (‘fetal well being’/exp OR peri*viability OR ‘newborn mortality’/exp OR ‘survival rate’/exp OR ‘survival’/exp OR surviv*:ti,ab OR ‘clinical outcome’/exp OR ‘pregnancy outcome’/exp OR ‘outcome parameter*’ OR ‘fetus outcome’/exp OR ‘outcome assessment’/exp OR ‘treatment outcome’/exp OR outcome*:ti,ab OR ‘neonatal intensive care unit’/exp OR ‘neonatal intensive care unit*’:ti,ab OR nicu:ti,ab) AND (‘biomedical technology assessment’/exp OR ‘technology assessment*’ OR hta:ti,ab)) AND [2013-2017]/py OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR ‘periviable birth*’ AND (‘fetal well being’/exp OR peri*viability OR ‘newborn mortality’/exp OR ‘survival rate’/exp OR ‘survival’/exp OR surviv*:ti,ab OR ‘clinical outcome’/exp OR ‘pregnancy outcome’/exp OR ‘outcome parameter*’ OR ‘fetus outcome’/exp OR ‘outcome assessment’/exp OR ‘treatment outcome’/exp OR outcome*:ti,ab OR ‘neonatal intensive care unit’/exp OR ‘neonatal intensive care unit*’:ti,ab OR nicu:ti,ab) AND (‘meta analysis’/de OR ‘systematic review’/de) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR ‘periviable birth*’ AND (‘fetal well being’/exp OR peri*viability OR ‘newborn mortality’/exp OR ‘survival rate’/exp OR ‘survival’/exp OR surviv*:ti,ab OR ‘clinical outcome’/exp OR ‘pregnancy outcome’/exp OR ‘outcome parameter*’ OR ‘fetus outcome’/exp OR ‘outcome assessment’/exp OR ‘treatment outcome’/exp OR outcome*:ti,ab OR ‘neonatal intensive care unit’/exp OR ‘neonatal intensive care unit*’:ti,ab OR nicu:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR ‘periviable birth*’ AND (‘fetal well being’/exp OR peri*viability OR ‘newborn mortality’/exp OR ‘survival rate’/exp OR ‘survival’/exp OR surviv*:ti,ab OR ‘clinical outcome’/exp OR ‘pregnancy outcome’/exp OR ‘outcome parameter*’ OR ‘fetus outcome’/exp OR ‘outcome assessment’/exp OR ‘treatment outcome’/exp OR outcome*:ti,ab OR ‘neonatal intensive care unit’/exp OR ‘neonatal intensive care unit*’:ti,ab OR nicu:ti,ab) AND (‘biomedical technology assessment’/exp OR ‘technology assessment*’ OR hta:ti,ab)) AND [1-1-2013]/sd)	126

#45	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('meta analysis'/de OR 'systematic review'/de) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('biomedical technology assessment'/exp OR 'technology assessment*' OR hta:ti,ab)) AND [1-1-2013]/sd	125
#44	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('meta analysis'/de OR 'systematic review'/de) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('biomedical technology assessment'/exp OR 'technology assessment*' OR hta:ti,ab)) AND [2013-2017]/py	119
#43	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('meta analysis'/de OR 'systematic review'/de) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)) OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('biomedical technology assessment'/exp OR 'technology assessment*' OR hta:ti,ab))	258
#42	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('biomedical technology assessment'/exp OR 'technology assessment*' OR hta:ti,ab)	11

#41	'biomedical technology assessment'/exp OR 'technology assessment*' OR hta:ti,ab	28,208
#40	hta:ti,ab	4,283
#39	'technology assessment*'	25,902
#38	'biomedical technology assessment'/exp	11,894
#37	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	249
#36	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab) AND ('meta analysis'/de OR 'systematic review'/de)	187
#35	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*' AND ('fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab)	5,231
#34	'fetal well being'/exp OR peri*viability OR 'newborn mortality'/exp OR 'survival rate'/exp OR 'survival'/exp OR surviv*:ti,ab OR 'clinical outcome'/exp OR 'pregnancy outcome'/exp OR 'outcome parameter*' OR 'fetus outcome'/exp OR 'outcome assessment'/exp OR 'treatment outcome'/exp OR outcome*:ti,ab OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab	3,571,194
#33	nicu:ti,ab	12,194
#32	'neonatal intensive care unit*':ti,ab	16,435
#31	'neonatal intensive care unit'/exp	1,955
#16	outcome*:ti,ab	1,792,313
#15	'treatment outcome'/exp	1,246,673
#14	'outcome assessment'/exp	368,514
#13	'fetus outcome'/exp	9,011
#12	'outcome parameter*'	5,899
#11	'pregnancy outcome'/exp	43,251
#10	'clinical outcome'/exp	19,256
#9	surviv*:ti,ab	1,265,430
#8	'survival'/exp	846,438
#7	'survival rate'/exp	195,585
#6	'newborn mortality'/exp	11,316
#5	peri*viability	39
#4	'fetal well being'/exp	2,650
#3	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable birth*'	9,461
#2	'periviable birth*'	44
#1	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab	9,425

Total: 126 Hits

Medline

Search Name: Outcomes of Extremely Preterm Birth (KH/MS)	
Search Date: 14/06/2017	
ID	Search, vid MEDLINE(R) <1946 to June Week 1 2017>, Ovid MEDLINE(R) Epub Ahead of Print <June 13, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 13, 2017>, Ovid MEDLINE(R) Daily Update <June 13, 2017>, Ovid MEDLINE(R) Versions
1	exp Infant, Extremely Premature/ (1238)
2	((extremely or very) adj2 ((prematur* or preterm or early) adj2 (newborn* or neonate* or baby or babies or toddler* or infant* or child* or birth* or deliver*))).mp. (6793)
3	peri?viable birth*.mp. (41)
4	1 or 2 or 3 (6815)
5	exp Fetal Viability/ (1716)
6	Peri?viability.mp. (25)
7	exp Survival/ (4514)
8	exp Survival Rate/ (152773)
9	surviv*.mp. (1203340)
10	exp Pregnancy Outcome/ (50342)
11	outcome parameter*.mp. (4012)
12	outcome*.mp. (1983314)
13	exp "Outcome Assessment (Health Care)"/ (911449)
14	exp Treatment Outcome/ (850061)
15	exp Intensive Care Units, Neonatal/ (11925)
16	neonatal intensive care unit*.mp. (13695)
17	NICU.ti,ab. (7562)
18	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (2910740)
19	4 and 18 (3796)
20	limit 19 to (meta analysis or systematic reviews) (251)
21	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/or Meta-Analysis.pt. (332932)
22	19 and 21 (249)
23	exp Technology Assessment, Biomedical/ (10264)
24	technology assessment*.mp. (12529)
25	HTA.ti,ab. (2260)
26	23 or 24 or 25 (14620)
27	19 and 26 (4)
28	20 or 22 or 27 (310)
29	limit 28 to yr="2013 –Current" (151)
30	limit 28 to ed=20130101-20170613 (131)
31	29 or 30 (159)
32	remove duplicates from 31 (145)

Total:145 Hits

8.3.2 Resources

Cochrane

Search Name: Extremely Prematurity_Resource Needs (KH/MS)	
Search Date: 14/06/2017	
ID	Search
#1	MeSH descriptor: [Infant, Extremely Premature] explode all trees
#2	((extreme* or very) near ((prematur* or preterm or early) near (newborn* or neonate* or baby or babies or toddler* or infant* or child* or birth* or deliver*))):ti,ab,kw (Word variations have been searched)
#3	periviable birth*:ti,ab,kw (Word variations have been searched)
#4	MeSH descriptor: [Fetal Viability] explode all trees
#5	Periviability:ti,ab,kw (Word variations have been searched)
#6	(limit* or threshold or border*) near viability:ti,ab,kw (Word variations have been searched)
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees
#9	neonatal intensive care unit*:ti,ab,kw (Word variations have been searched)
#10	NICU:ti,ab,kw (Word variations have been searched)
#11	MeSH descriptor: [Intensive Care, Neonatal] explode all trees
#12	#8 or #9 or #10 or #11
#13	#7 and #12
#14	MeSH descriptor: [Health Planning] explode all trees
#15	care planning:ti,ab,kw (Word variations have been searched)
#16	MeSH descriptor: [Hospital Bed Capacity] explode all trees
#17	MeSH descriptor: [Length of Stay] explode all trees
#18	MeSH descriptor: [Health Resources] explode all trees
#19	MeSH descriptor: [Resource Allocation] explode all trees
#20	resource*:ti,ab,kw (Word variations have been searched)
#21	hospital capacit*:ti,ab,kw (Word variations have been searched)
#22	adequate care:ti,ab,kw (Word variations have been searched
#23	appropriate care:ti,ab,kw (Word variations have been searched)
#24	MeSH descriptor: [Health Services Needs and Demand] explode all trees
#25	MeSH descriptor: [Health Personnel] explode all trees and with qualifier(s): [Organization & administration – OG, Standards – ST]
#26	health near (worker* or workforce or work-force or personnel or staff or manpower or professional):ti,ab,kw (Word variations have been searched)
#27	(nurse* or midwife or midwives or doctor* or physician* or carer* or practitioner*):ti,ab,kw (Word variations have been searched)
#28	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#29	#13 and #28 Publication Year from 2007 to 2017

Total: 46 Hits

CRD

Search Name: Outcomes of Extremely Preterm Birth (KH/MS)	
Search Date: 14/06/2017	
ID	Search
1	MeSH DESCRIPTOR Infant, Extremely Premature EXPLODE ALL TREES
2	(((extremely or very) NEAR ((prematur* or preterm or early) NEAR (newborn* or neonate* or baby or babies or toddler* or infant* or child* or birth* or deliver*))))
3	(peri*viable birth*)
4	MeSH DESCRIPTOR Fetal Viability EXPLODE ALL TREES
5	(Peri*viability)
6	MeSH DESCRIPTOR Intensive Care Units, Neonatal EXPLODE ALL TREES
7	(neonatal intensive care unit*)
8	(NICU)
9	MeSH DESCRIPTOR Intensive Care, Neonatal EXPLODE ALL TREES
10	MeSH DESCRIPTOR Health Planning EXPLODE ALL TREES
11	(care planning)
12	MeSH DESCRIPTOR Hospital Bed Capacity EXPLODE ALL TREES
13	MeSH DESCRIPTOR Length of Stay EXPLODE ALL TREES
14	MeSH DESCRIPTOR Health Resources EXPLODE ALL TREES
15	MeSH DESCRIPTOR Resource Allocation EXPLODE ALL TREES
16	(resource*)
17	(hospital capacit*)
18	(adequate care)
19	(appropriate care)
20	MeSH DESCRIPTOR Health Services Needs and Demand EXPLODE ALL TREES
21	MeSH DESCRIPTOR Health Personnel EXPLODE ALL TREES WITH QUALIFIERS OG, ST, UT
22	(health NEAR (worker* OR workforce OR work-force OR personnel OR staff OR manpower OR professional))
23	(nurse* OR midwife OR midwives OR doctor* OR physician* OR carer* OR practitioner*)
24	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25	* WHERE LPD FROM 01/01/2007 TO 14/06/2017
26	MeSH DESCRIPTOR Infant Care EXPLODE ALL TREES
27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #26
28	#24 AND #27
29	* FROM 2007 TO 2017
30	#25 OR #29
31	#28 AND #30

Total: 61 Hits

Embase

Search Name: Outcomes of Extremely Preterm Birth (KH/MS)		
Search Date: 14/06/2017		
No.	Query Results	Results
#40	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable*':ti,ab OR peri*viability OR ((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab AND ('neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab OR 'newborn intensive care'/exp OR 'infant care'/exp) AND ('health care planning'/exp OR 'care planning':ti,ab OR 'hospital bed capacity'/exp OR 'length of stay'/exp OR 'resource allocation'/exp OR resource*:ti,ab OR 'hospital capacit*':ti,ab OR 'adequate care':ti,ab OR 'appropriate care':ti,ab OR 'health care personnel'/mj OR (health NEAR/1 (worker* OR workforce OR 'work force' OR personnel OR staff OR manpower OR professional)):ti,ab OR nurse*:ti,ab OR midwife:ti,ab OR midwives:ti,ab OR doctor*:ti,ab OR physician*:ti,ab OR carer*:ti,ab OR practitioner*:ti,ab) AND [2007-2017]/py OR (((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable*':ti,ab OR peri*viability OR ((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab AND ('neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab OR 'newborn intensive care'/exp OR 'infant care'/exp) AND ('health care planning'/exp OR 'care planning':ti,ab OR 'hospital bed capacity'/exp OR 'length of stay'/exp OR 'resource allocation'/exp OR resource*:ti,ab OR 'hospital capacit*':ti,ab OR 'adequate care':ti,ab OR 'appropriate care':ti,ab OR 'health care personnel'/mj OR (health NEAR/1 (worker* OR workforce OR 'work force' OR personnel OR staff OR manpower OR professional)):ti,ab OR nurse*:ti,ab OR midwife:ti,ab OR midwives:ti,ab OR doctor*:ti,ab OR physician*:ti,ab OR carer*:ti,ab OR practitioner*:ti,ab) AND [1-1-2007]/sd)	227
#39	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable*':ti,ab OR peri*viability OR ((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab AND ('neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab OR 'newborn intensive care'/exp OR 'infant care'/exp) AND ('health care planning'/exp OR 'care planning':ti,ab OR 'hospital bed capacity'/exp OR 'length of stay'/exp OR 'resource allocation'/exp OR resource*:ti,ab OR 'hospital capacit*':ti,ab OR 'adequate care':ti,ab OR 'appropriate care':ti,ab OR 'health care personnel'/mj OR (health NEAR/1 (worker* OR workforce OR 'work force' OR personnel OR staff OR manpower OR professional)):ti,ab OR nurse*:ti,ab OR midwife:ti,ab OR midwives:ti,ab OR doctor*:ti,ab OR physician*:ti,ab OR carer*:ti,ab OR practitioner*:ti,ab) AND [1-1-2007]/sd	227
#38	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable*':ti,ab OR peri*viability OR ((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab AND ('neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab OR 'newborn intensive care'/exp OR 'infant care'/exp) AND ('health care planning'/exp OR 'care planning':ti,ab OR 'hospital bed capacity'/exp OR 'length of stay'/exp OR 'resource allocation'/exp OR resource*:ti,ab OR 'hospital capacit*':ti,ab OR 'adequate care':ti,ab OR 'appropriate care':ti,ab OR 'health care personnel'/mj OR (health NEAR/1 (worker* OR workforce OR 'work force' OR personnel OR staff OR manpower OR professional)):ti,ab OR nurse*:ti,ab OR midwife:ti,ab OR midwives:ti,ab OR doctor*:ti,ab OR physician*:ti,ab OR carer*:ti,ab OR practitioner*:ti,ab) AND [2007-2017]/py	223
#37	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable*':ti,ab OR peri*viability OR ((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab AND ('neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab OR 'newborn intensive care'/exp OR 'infant care'/exp) AND ('health care planning'/exp OR 'care planning':ti,ab OR 'hospital bed capacity'/exp OR 'length of stay'/exp OR 'resource allocation'/exp OR resource*:ti,ab OR 'hospital capacit*':ti,ab OR 'adequate care':ti,ab OR 'appropriate care':ti,ab OR 'health care personnel'/mj OR (health NEAR/1 (worker* OR workforce OR 'work force' OR personnel OR staff OR manpower OR professional)):ti,ab OR nurse*:ti,ab OR midwife:ti,ab OR midwives:ti,ab OR doctor*:ti,ab OR physician*:ti,ab OR carer*:ti,ab OR practitioner*:ti,ab)	288
#36	'health care planning'/exp OR 'care planning':ti,ab OR 'hospital bed capacity'/exp OR 'length of stay'/exp OR 'resource allocation'/exp OR resource*:ti,ab OR 'hospital capacit*':ti,ab OR 'adequate care':ti,ab OR 'appropriate care':ti,ab OR 'health care personnel'/mj OR (health NEAR/1 (worker* OR workforce OR 'work force' OR personnel OR staff OR manpower OR professional)):ti,ab OR nurse*:ti,ab OR midwife:ti,ab OR midwives:ti,ab OR doctor*:ti,ab OR physician*:ti,ab OR carer*:ti,ab OR practitioner*:ti,ab	1,436,734
#35	nurse*:ti,ab OR midwife:ti,ab OR midwives:ti,ab OR doctor*:ti,ab OR physician*:ti,ab OR carer*:ti,ab OR practitioner*:ti,ab	931,089
#34	(health NEAR/1 (worker* OR workforce OR 'work force' OR personnel OR staff OR manpower OR professional)):ti,ab	34,479
#33	'health care personnel'/mj	22,509

#32	'appropriate care':ti,ab	4,022
#31	'adequate care':ti,ab	1,202
#30	'hospital capacit*':ti,ab	287
#29	resource*:ti,ab	307,622
#28	'resource allocation'/exp	17,816
#27	'length of stay'/exp	129,577
#26	'hospital bed capacity'/exp	18,598
#25	'care planning':ti,ab	6,368
#24	'health care planning'/exp	88,839
#23	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable*':ti,ab OR peri*viability OR ((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab AND ('neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab OR 'newborn intensive care'/exp OR 'infant care'/exp)	1,648
#22	'neonatal intensive care unit'/exp OR 'neonatal intensive care unit*':ti,ab OR nicu:ti,ab OR 'newborn intensive care'/exp OR 'infant care'/exp	35,771
#21	'infant care'/exp	252
#20	'newborn intensive care'/exp	25,172
#19	nicu:ti,ab	12,194
#18	'neonatal intensive care unit*':ti,ab	16,435
#17	'neonatal intensive care unit'/exp	1,955
#16	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab OR 'periviable*':ti,ab OR peri*viability OR ((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab	9,732
#6	((limit* OR threshold* OR border*) NEAR/1 viability):ti,ab	197
#5	peri*viability	39
#2	'periviable*':ti,ab	137
#1	((extreme* OR very) NEAR/3 (prematur* OR preterm OR early) NEAR/3 (newborn* OR neonate* OR baby OR babies OR toddler* OR infant* OR child* OR birth* OR deliver*)):ti,ab	9,425

Total: 227 Hits

Medline

Search Name: Outcomes of Extremely Preterm Birth (KH/MS)	
Search Date: 14/06/2017	
ID	Search
1	exp Infant, Extremely Premature/ (1238)
2	((extremely or very) adj2 ((prematur* or preterm or early) adj2 (newborn* or neonate* or baby or babies or toddler* or infant* or child* or birth* or deliver*))).mp. (6793)
3	peri?viable.mp. (105)
4	peri?viability.mp. (25)
5	((limit* or threshold* or border*) adj2 viability).mp. (619)
6	1 or 2 or 3 or 4 or 5 (7344)
7	exp Intensive Care Units, Neonatal/ (11925)
8	neonatal intensive care unit*.mp. (13695)
9	exp Intensive Care, Neonatal/ (5065)
10	exp Infant Care/ (12961)
11	NICU.ti,ab. (7562)
12	7 or 8 or 9 or 10 or 11 (36847)
13	6 and 12 (1354)
14	exp Health Planning/ (321144)

15	care planning.mp. (42333)
16	exp Hospital Bed Capacity/ (23760)
17	exp "Length of Stay"/ (74003)
18	exp Health Resources/ (22935)
19	exp Resource Allocation/ (16500)
20	resource*.mp. (301935)
21	hospital capacit*.mp. (212)
22	adequate care.mp. (960)
23	appropriate care.mp. (3188)
24	exp "Health Services Needs and Demand"/ (56323)
25	exp *Health Personnel/og, st, ut [Organization & Administration, Standards, Utilization] (37588)
26	(health adj2 (worker* or workforce or work-force or personnel or staff or manpower)).mp. (195297)
27	(nurse* or midwife or midwives or doctor* or physician* or carer* or practitioner*).mp. (959052)
28	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (1647417)
29	13 and 28 (289)
30	remove duplicates from 29 (280)
31	limit 30 to yr="2007-2017" (177)
32	limit 30 to ed=20070101-20170614 (172)

Total: 172 Hits

Ludwig Boltzmann Institut
Health Technology Assessment