

# The Value of Autopsy in Preterm Infants At A Swedish Tertiary Neonatal Intensive Care Unit 2002-2018

**Alice Hoffsten**

Uppsala University

**Laszlo Markasz**

Uppsala University

**Katharina Ericson**

Uppsala University Hospital

**Leif D Nelin**

Ohio State University College of Medicine, Columbus, Ohio, USA

**Richard Sindelar** (✉ [richard.sindelar@kbh.uu.se](mailto:richard.sindelar@kbh.uu.se))

Uppsala University

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# **The Value of Autopsy in Preterm Infants at a Swedish Tertiary Neonatal Intensive Care Unit 2002-2018**

Alice Hoffsten MD<sup>1</sup>, Laszlo Markasz MD PhD<sup>1,2</sup>, Katharina Ericson MD<sup>3</sup>, Leif D Nelin MD<sup>1,4</sup> and Richard Sindelar MD PhD<sup>1,2</sup>

<sup>1</sup>Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

<sup>2</sup>Neonatology Division, Uppsala University Children's Hospital, Uppsala, Sweden

<sup>3</sup>Department of Pathology, Uppsala University Hospital, Uppsala, Sweden

<sup>4</sup>Nationwide Children's Hospital, Ohio State University College of Medicine, Columbus, Ohio, USA

**Running title:** Causes of Death and the Value of Autopsy in Preterms

**Corresponding author:** Richard Sindelar, Department of Women's and Children's Health, University Children's Hospital, SE-751 85 Uppsala, Sweden. Phone: +46-18-611 96 27. Fax +46-18-611 58 26

**Email:** [richard.sindelar@kbh.uu.se](mailto:richard.sindelar@kbh.uu.se)

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**Abbreviations:** BPD, Bronchopulmonary Dysplasia; COD, Cause of Death; IVH, Intraventricular

Hemorrhage; MDC, Medical Death Certificate; NEC, Necrotizing Enterocolitis; RDS, Respiratory

Distress Syndrome; SNQ, Swedish Neonatal Quality Registry; UUCH, Uppsala University Children's

Hospital

## **ABSTRACT**

Reliable data on causes of death (COD) in preterm infants is needed to assess perinatal care and current clinical guidelines. In this retrospective observational analysis of all deceased preterm infants born <37 weeks' gestational age (n=278; 2012-2018) at a Swedish tertiary neonatal intensive care unit, we compared preliminary COD from Medical Death Certificates with autopsy defined COD (2002-2018), and assessed changes in COD between two periods (Period 1: 2002-2009 vs Period 2: 2011-2018). Autopsy was performed in 73% of all cases and was more than twice as high compared to national rates of infant autopsies in Sweden (33%). Autopsy defined COD differed from preliminary COD in 34.9% of the cases. Necrotizing enterocolitis (NEC) as COD increased between Period 1 and 2 (5% vs 26%), while intraventricular hemorrhage decreased (13% vs 6%). The autopsy rate did not change between the two study periods (75% vs 71%). We conclude that autopsy changed the preliminary COD in a third of cases, while the incidence of NEC as COD increased markedly during the study period. Since there is a high risk to determine COD incorrectly based solely on clinical findings in preterm infants, autopsy remains a valuable method to obtain reliable COD.

## INTRODUCTION

The autopsy has been fundamental to understand anatomy and pathophysiology in medicine and neonatology. Despite proactive obstetric and neonatal care, prematurity remains the most common worldwide cause of death (COD) among children under the age of five years <sup>1,2</sup>. As autopsy is “the gold standard” for accurately determining COD, autopsy contributes to the continued development of neonatal care and possibly improved survival in preterm infants <sup>3,4</sup>.

When reporting causes of death, it is customary to use the International Classification of Diseases (ICD) by the WHO <sup>5</sup>. To assign prematurity as the COD is not recommended by the WHO, unless no other COD can be confirmed. Despite these recommendations, there has been a continued use of prematurity as COD instead of defining the specific COD <sup>6-8</sup>. In mortality reports, ICD-codes are grouped into categories to provide coherent descriptions, although, classification systems often differ between reports and/or countries. Based on Wigglesworth’s classification of perinatal mortality <sup>9</sup>, the International Collaborative Effort (ICE) offered a classification method for infant mortality in 1989 to enable international comparisons <sup>10</sup>. Still, reports continue to use different classifications <sup>11-14</sup>, and some, including the ICE, use the classification of prematurity related deaths despite the recommendations from the WHO <sup>8</sup>. New classification systems have been proposed, yet no consensus has been reached <sup>15,16</sup>. In Sweden, death is certified in two stages: the Notification of Death and the Medical Death Certificate (MDC) <sup>6</sup>. Writing a MDC to define COD utilizes the WHO guidelines. A chronology of events leading to death is listed in the MDC, including the duration of each condition. The direct COD is defined as the final condition causing death <sup>5,6</sup>.

Unfortunately, there is a global trend for decreasing autopsy rates in infants <sup>17</sup>, which has also been seen in Sweden. A report from 2014 showed that infant autopsy rates had decreased from 71% to 35% for boys and from 64% to 31% for girls since 1987 <sup>7</sup>. The

former chief editor of JAMA George Lundberg warned in 1988 that autopsy reduction will negatively affect provided care, since lack of quality control of care will result in reduced knowledge of beneficial or negative effects of treatments <sup>18</sup>. Accurately defined COD reports are also needed for reliable and meaningful statistics. Records of preterm deaths are frequently incorrect, with flaws in the definition of live births, underreporting of births and deaths, and inaccurately stated CODs <sup>19</sup>. Some have advocated for postmortem MRI as a supplement to autopsies <sup>20,21</sup>. Although MRI brings some diagnostic value, it has been shown to miss more than half of the findings an autopsy would have provided, and neglects histological and microbiological features <sup>20,21</sup>.

The aim of this study was to compare the preliminary COD to autopsy records in an effort to validate the preliminary COD and define the incidence of autopsy among preterm infants treated in our NICU between 2002 and 2018. We also wanted to determine if there have been changes in the COD over time. A better understanding of the significance of accurately determining the COD by autopsy may lead to the development of standardized protocols for defining COD.

## RESULTS

The mortality for all premature infants born in Uppsala was 3.8% during Period 1 and 5.0% during Period 2 ( $p=0.059$ ). No differences in birth weight, gestational age, degree of immaturity or age at death was found between the two periods (Table 2). There was a higher percentage of boys who died in Period 2.

Autopsy data are summarized in Table 3. The autopsy rate over the whole study period was 73.0%, and did not change between the study periods (75% vs 71%). Boys were autopsied in 70.2% of cases and girls in 76.9%. The main reason for an autopsy not being performed was parental refusal ( $n=61/75$ ; 81.3%). In 14.7% cases, there was no declared reason for autopsy not being performed. The frequency of autopsies was lower in those who died after 7 days of life (64.9%) as compared to those who died earlier (78.1%). Postmortem examinations changed the preliminary COD or confirmed the suspected COD in 35.0 % of all autopsied cases (23.7% of the preliminary CODs were revised completely, and 11.3% of the suspected CODs were confirmed). In 5% of the autopsied cases it was not possible to define if autopsy altered the COD, due to lack of data on the preliminary COD.

### *Cause of Death – Comparison between Period 1 and Period 2*

NEC as the COD increased from 5.0% to 25.2% ( $p<0.001$ ) from Period 1 to Period 2, whereas IVH as the COD decreased ( $p=0.042$ ) (Table 4). The annual incidence of NEC as a COD is shown in Figure 2. Period 2 had fewer cases with chromosomal anomalies ( $p=0.029$ ), perinatal asphyxia ( $p=0.033$ ), and RDS ( $p=0.039$ ) as the COD than in Period 1. The isolated spontaneous intestinal perforations ( $n=4$ ) were either consequences of anomalies or perforation without NEC.

### *Cause versus Timing of Death*

As shown in Figure 3a, fewer patients died due to perinatal asphyxia between day 1-6 ( $p=0.050$ ) in Period 2 than in Period 1. Cases with NEC as the COD increased for infants who died on days 7-28 and after 28 days ( $p=0.001$  and  $p=0.025$ , respectively), while infection as the COD decreased ( $p=0.006$ ) between Period 1 and 2 for those infants who died on days 7-28. Median days of life for patients with NEC as cause of death was 4 (IQR=8.5) in Period 1 and 11 (IQR=11.5) in Period 2 ( $p=0.023$ ).

### *Cause of death versus Degree of Immaturity*

As presented in Figure 3b, the incidence of NEC as a COD in Period 2 was greater than in Period 1 for very preterm ( $p=0.028$ ) and extremely preterm infants ( $p<0.001$ ). There were no other significant differences in COD in the gestational age groups between Periods 1 and 2 (Figure 3b).

## DISCUSSION

In this study involving 278 preterms who all received proactive care, regardless of gestational age, we found an autopsy rate of 73%. The rate was comparable between sexes, 77.0% of girls and 70.2% of boys. The autopsy rate in this cohort was more than twice as high compared to national rates of infant autopsies in Sweden <sup>7</sup>. This is likely due to the program to increase autopsy rates in preterm infants at UUCH. Infants who died at an older age were autopsied less frequently than those who died at a younger age. Although unclear from this study, this difference in autopsy rates depending on age may be a consequence of there being time to find a definitive diagnosis and therefore an autopsy not being deemed necessary. Parents refusing to consent to autopsy was the main reason for autopsies not taking place, which is in agreement with previous findings <sup>21,22</sup>. Lack of parental consent may be secondary to lack of information provided regarding the procedure and potential benefit of an autopsy. In many cases, the responsibility for obtaining consent for autopsy lies with the medical staff who may not fully understand the importance of the autopsy when discussing the procedure with the parents <sup>22,23</sup>. For a family, the correct COD for a lost child may be very important since knowledge of genetic anomalies or syndromes, which can be very difficult to diagnose solely on clinical exam in very preterm infants, may help in future pregnancy decisions <sup>21</sup>.

Our main finding is that post-mortem examinations contributed considerably to determining the COD as evidenced by altering the preliminary COD in a third of cases. This is consistent with results from previous studies, where a percentage of 25-36% CODs were found to be altered by autopsy in centers with generally low autopsy rates <sup>21,22,24</sup>. A higher autopsy rate might be expected to decrease the number of times the preliminary COD is changed, given that in studies with lower autopsy rates, the autopsy is performed when the COD is unclear to the clinician <sup>17,21,25</sup>. However, as shown in this study, even with relatively high autopsy rates the chance of changing the preliminary COD remains high. Thus, our data

are consistent with the notion that improving autopsy rates will yield a higher quality of COD and therefore be more useful in understanding COD trends in the NICU.

The decrease of IVH as a COD overtime is consistent with national findings in Sweden<sup>26</sup> and may be attributable to refined ventilation strategies<sup>27</sup> and more consistent treatment with antenatal corticosteroids<sup>28</sup>. It is also possible that IVH may no longer cause death due to improvements in life-support measures following IVH and thus move IVH from a COD to a co-morbidity. We found that the incidence of congenital anomalies as a COD in our cohort was lower than in other comparable studies in high income countries<sup>29</sup>. One possible explanation could be the screening for congenital anomalies and Swedish abortion practices. Perhaps a more likely reason could be the targeting of a more precise COD rather than simply assigning an umbrella diagnosis like congenital anomalies as the primary COD. Interestingly, the occurrence of NEC as the COD was significantly greater during Period 2 as compared to Period 1. The increase of NEC was especially evident in extremely preterm infants and deaths during day 7-28 and after 28 days of life. This is likely due to NEC being a disorder typically occurring after 1-2 of weeks of life<sup>30</sup> and that the risk of NEC increases with decreasing gestational age at birth<sup>31</sup>. Another potential factor in the overall increase of NEC as a COD could be that improvements in clinical care over time enable the child to survive long enough to develop NEC as has been suggested previously<sup>32</sup>. The median age at death for patients with NEC as COD increased significantly between Period 1 and Period 2. Another potential explanation could be case clustering of NEC as has been described where viral or bacterial outbreaks (so called epidemic NEC) contribute to overall NEC incidence<sup>33,34</sup>. It is clear that the increase in NEC as a COD cannot be simply ascribed to more autopsies allowing more detailed diagnosis, since the autopsy rate was similar during both periods.

The retrospective observational study design is logical for this type of study and more than satisfactorily captures prevalence of different COD and the value of autopsy in

determining COD. However, given the observational design it is impossible to draw conclusions regarding the causes of the changes in COD, particularly NEC, seen over time. Further research is needed to uncover the causes of the differences in COD between the two periods. Structured national and international surveying of neonatal care is increasing worldwide<sup>35</sup>, which could have a huge impact on understanding COD and changes in COD over time. Some other studies on infant mortality have systematically assigned prematurity as the major COD<sup>13</sup> ignoring the recommendations of the WHO<sup>8</sup>. We found 10 cases in this cohort where prematurity was registered as the COD, however 7 of them could later be sorted into other categories using data from medical records and/or autopsies. Only in 3 out of 278 cases did prematurity remain as the final COD. The low rate of prematurity as COD demonstrates the feasibility of following the WHO recommendation regarding not assigning prematurity as the primary COD. Some of the complications of prematurity are difficult to diagnose in preterm infants, since symptoms may not be specific or may appear after a delay. In our study, nearly 75% of all diagnoses were autopsy-verified substantiating the COD. All autopsies were performed by the same pathologist, which results in a high level of qualitative continuity. In addition, the neonatologist involved in the patient's care attended the postmortem examination, thereby providing the pathologist with more detailed pre-mortem clinical findings, which facilitated examinations and supported COD determination.

This study highlights the importance of post-mortem examinations, which continue to yield valuable information and contribute to confirming actual COD in preterm infants. Besides observing an increase in NEC and decrease in IVH between the two periods, we found that the results from the autopsy changed the preliminary COD in a third of cases during the entire study period. It's interesting that 73% of all deceased preterm infants in this cohort were autopsied and not only the ones with uncertain diagnoses. Our findings suggest that it would be beneficial to reverse the negative trend in autopsy rates. This cohort demonstrates that a positive attitude toward autopsy and a good cooperation between the

pathologist and the neonatologist can promote relatively high autopsy rates, and subsequent reliable COD data.

## **METHODS**

### *Study setting and ethical consideration*

This study is a retrospective observational study of all preterm patient deaths from 2002 to 2018 and a 2-period sub-analysis (2002-2009 vs 2011-2018) on ward 95F, a tertiary NICU at Uppsala University Children's Hospital (UUCH). The study has been approved by the Regional Ethical Review Board of Uppsala, D:nr 2019-05033, and by the Uppsala Biobank, D:nr BbA-827-2019-094. Data were de-identified before analysis, according to operative ethical regulations.

### *Inclusion of Participants*

Figure 1 shows a flowchart of the selection of participants. All live born infants admitted to and who subsequently died on 95F during the period of 2002 to 2018 were extracted from the Swedish Neonatal Quality Registry (SNQ) (n=356). To study solely infant mortality, patients who died after one year of age were excluded (n=1). Term infants ( $\geq 37$  weeks gestation) were excluded (n=77). Thus, there were a total of 278 infants that met inclusion criteria and had none of the exclusion criteria.

For the comparison between preliminary COD and definitive COD according to autopsy, there were 203 infants with an autopsy (Figure 1). Medical Death Certificate (MDCs) were examined to determine preliminary cause of death. If multiple MDCs were issued, the MDC issued prior to autopsy was used to avoid the preliminary COD being influenced by autopsy findings. If the MDC was issued after autopsy findings, the discharge note was examined to determine the presumed COD prior to autopsy. MDC and the discharge note were written by the attending physician well acquainted with the patient, and confirmed by the head physician in charge of the ward. An autopsy included a macroscopic review of tissues with a neonatologist present, immune-histological analysis linked to symptomology,

bacterial cultures and PCR-analysis if suspicion for viral infection from clinical symptoms or from macroscopic findings was present. The present neonatologist provided clinical data, contributing to the definitive cause of death as determined by autopsy. All infant autopsies were performed by the same pathologist and none was restricted in scope. Parental consent was required for autopsy. For the individuals who were not autopsied, the reason for an autopsy not being performed was defined.

### *Data Extraction and Study Variables*

Perinatal and postnatal data were collected from the SNQ. Perinatal data included time of birth, GA, sex, and birth weight. GA was documented as complete weeks and days, determined by ultrasound. Postnatal data included whether autopsy was performed or not, days of life, and if recorded, why an autopsy was not performed. If the autopsy was not performed due to parental reluctance no retrospective inquiry was performed, since this was considered ethically inappropriate. Missing data in SNQ were complemented by retrieving Medical Death Certificates (MDC) and charts from Cosmic® (electronic journal database after 2008) or from Regional archives (before 2008). Autopsy records were collected from the pathology chart system Sympathy®. Premature birth rates for the Uppsala Region were obtained from SNQ. Cause of death was determined according to ICD-10 codes<sup>8</sup>. Definitive COD was determined from autopsy records for those who underwent autopsy (n=203). For the rest (n=75), MDCs and discharge notes were used for definitive COD. Causes of death were categorized by groups based on ICE<sup>10</sup> and further refined in alignment with categories used in recent publications<sup>11-13</sup>. The final categories are presented in Table 1. The categories were established prior to data collection, to avoid the categorization being influenced by the data. Definitions of COD are described in Supplement 1.

For autopsied infants, MDCs were examined to compare preliminary and definitive COD. If

the MDC was issued after autopsy findings, the discharge note was examined to determine the presumed COD prior to autopsy. The preliminary COD and the definitive COD were compared to see if the definitive COD was altered due to information arising from the autopsy. The outcome after autopsy could be one of three: no change of COD; revised COD; or confirmed suspected but not yet established COD. Suspected COD could for instance be a suspected infection, but without positive cultures or identification of the location of the infection. If COD from the autopsy was “Prematurity” (n=10), but the clinicians found a more precise COD, the more precise COD was used as the definitive COD, in line with the recommendations from the WHO <sup>8</sup>.

### *Statistical Analyses*

Descriptive statistics were calculated in Excel, Version 15.27 (161010). The rest of the statistical analysis was performed in SPSS version 26. A p-value <0.05 was considered significant. Comparisons between groups for continuous data were done using the Mann-Whitney U-test. For trend difference analysis in COD from 2002-2009 (n=105) and 2011-2018 (n=160), both autopsied and not autopsied infants were included. A chi-square test was used to compare the frequency of each diagnosis between the two periods. The comparison between preliminary COD and definitive COD according to autopsy was performed on autopsied individuals from 2002-2018 (n=203).

## **AVAILABILITY OF MATERIALS AND DATA**

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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## **COMPETING INTERESTS**

The authors declare no competing interests.

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## **AUTHORS' CONTRIBUTION**

AH performed the collection of data, statistical analysis, wrote and edited the manuscript. LM contributed through data analysis, writing and revising of the manuscript. KE performed all autopsies included in this study and assisted in data collection. LDN partook in data analysis as well as writing and revising the manuscript. RS was the one to set up the study and further partook in data collection, data analysis, writing and revising of the manuscript. The manuscript has been read and approved for submission by all authors.

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## FIGURE LEGENDS

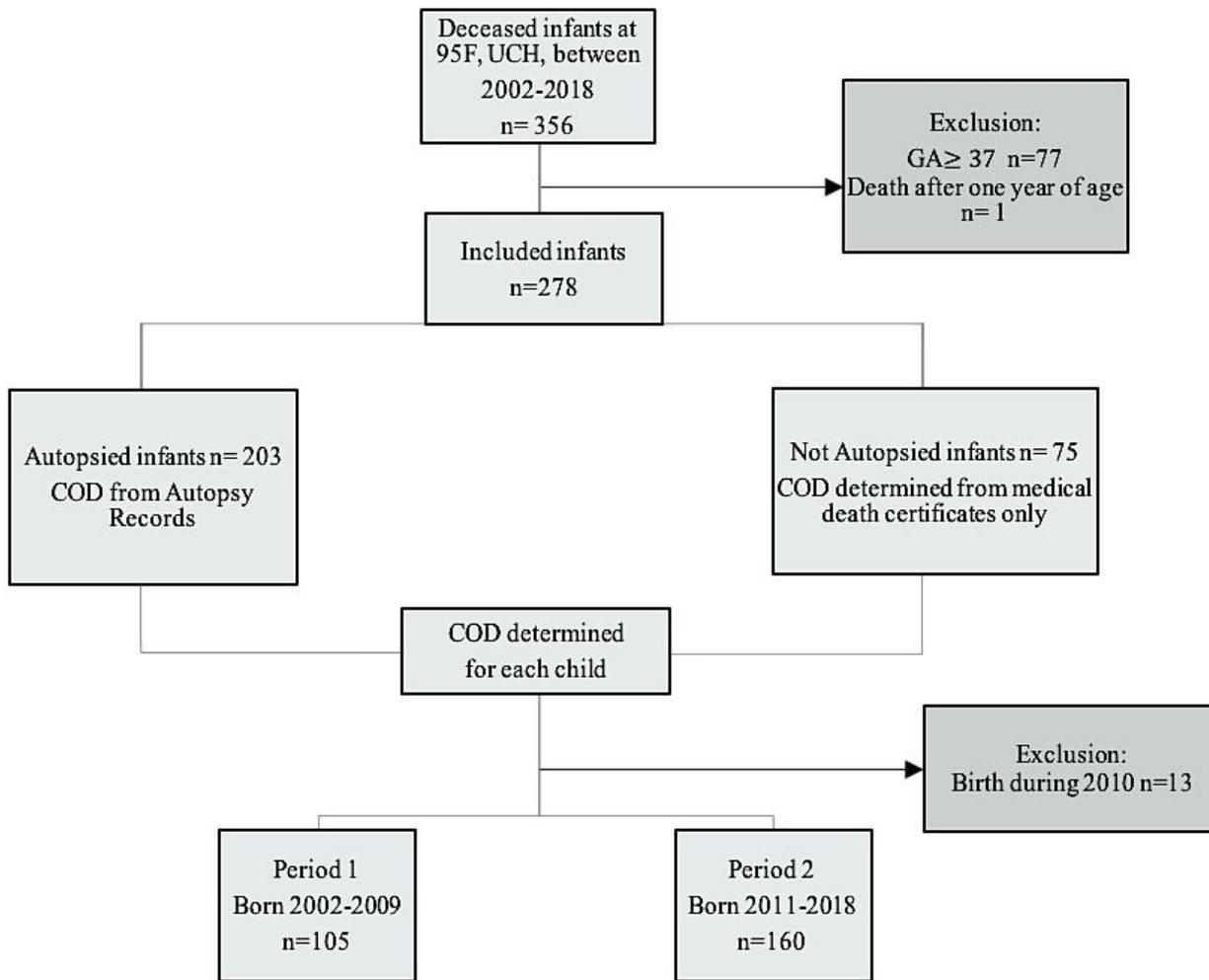
**Figure 1.** Inclusion of participants, data extraction and period division

**Figure 2.** Annual incidence of NEC as cause of death from 2002 to 2018.

**Figure 3a.** Distribution in percent of causes of death at various time intervals (0-24 hours; 1-6 days; 7-28 days; >28 days) during Period 1 and Period 2. \*  $p < 0.05$ ; significant change between Period 1 and Period 2 within each time interval. Congenital, congenital anomalies; Respiratory, respiratory causes; IVH, intraventricular hemorrhage; Infection, infection with septicemia; NEC, necrotizing enterocolitis. See Table 1 and Supplement 1 for further categorization and definition of causes of death.

**Figure 3b.** Distribution in percent of causes of death at various degrees of immaturity (gestational age <28 weeks, 28-31 weeks and 32-36 weeks) during Period 1 and Period 2. \*  $p < 0.05$ ; significant change between Period 1 and Period 2 within each degree of immaturity. GA; gestational age; Congenital, congenital anomalies; Respiratory, respiratory causes; IVH, intraventricular hemorrhage; Infection, infection with septicemia; NEC, necrotizing enterocolitis. See Table 1 and Supplement 1 for further categorization and definition of causes of death.

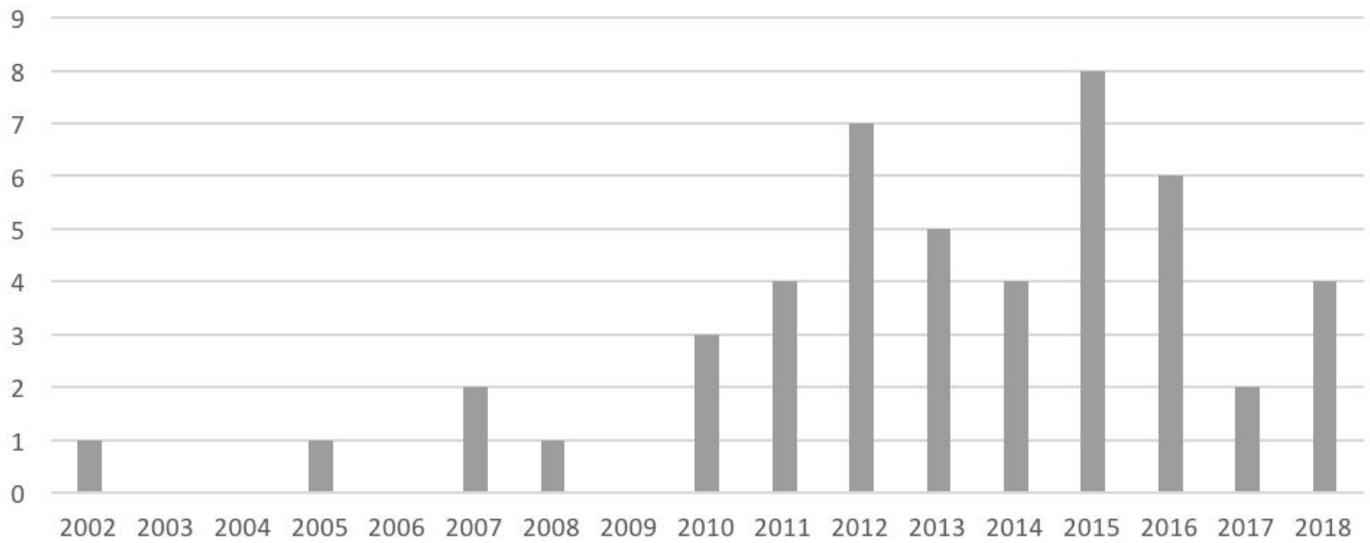
# Figures



**Figure 1**

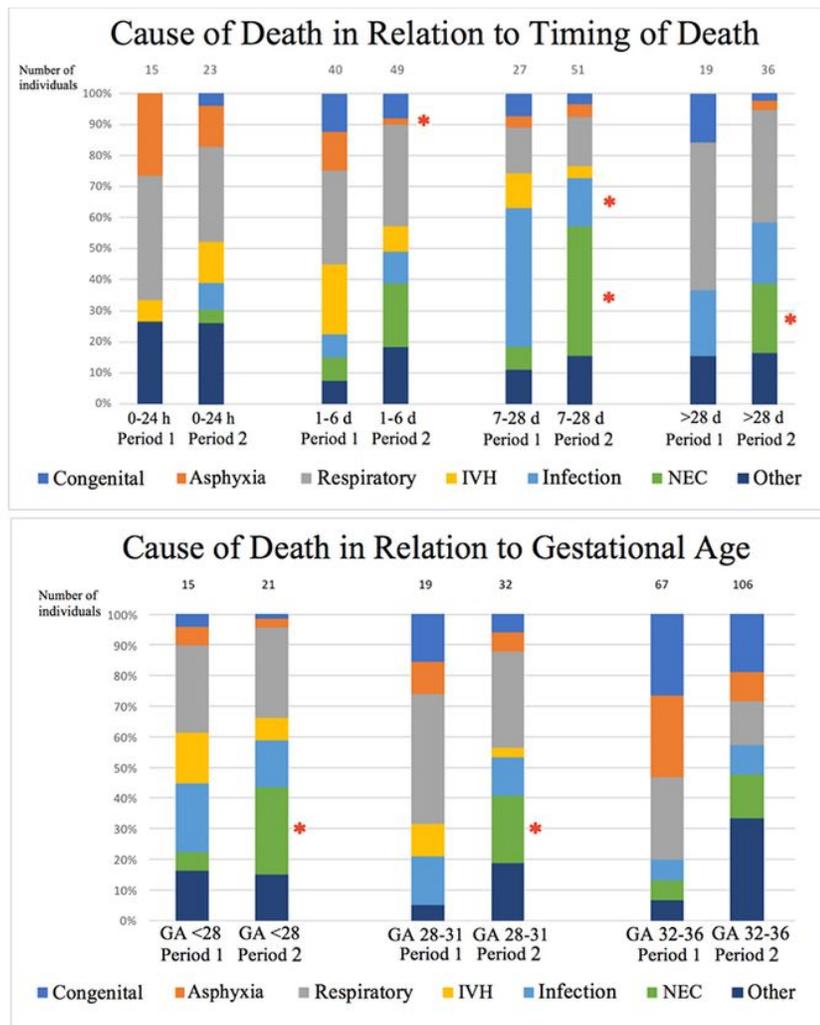
Inclusion of participants, data extraction and period division

# Annual Incidence of NEC as Cause of Death



**Figure 2**

Annual incidence of NEC as cause of death from 2002 to 2018.



**Figure 3**

3a. Distribution in percent of causes of death at various time intervals (0-24 hours; 1-6 days; 7-28 days; >28 days) during Period 1 and Period 2. \*  $p < 0.05$ ; significant change between Period 1 and Period 2 within each time interval. Congenital, congenital anomalies; Respiratory, respiratory causes; IVH, intraventricular hemorrhage; Infection, infection with septicemia; NEC, necrotizing enterocolitis. See Table 1 and Supplement 1 for further categorization and definition of causes of death. 3b. Distribution in percent of causes of death at various degrees of immaturity (gestational age <28 weeks, 28-31 weeks and 32-36 weeks) during Period 1 and Period 2. \*  $p < 0.05$ ; significant change between Period 1 and Period 2 within each degree of immaturity. GA; gestational age; Congenital, congenital anomalies; Respiratory, respiratory causes; IVH, intraventricular hemorrhage; Infection, infection with septicemia; NEC, necrotizing enterocolitis. See Table 1 and Supplement 1 for further categorization and definition of causes of death.

## Supplementary Files

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