An International Comparison of Death Classification at 22 to 25 Weeks Gestational Age

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Abbreviations: United Kingdom (UK); United States (US); Neonatal intensive care unit (NICU).
Table of Contents Summary: Comparison of seven countries showed variation in survival for births at 22-23 weeks arises in part from differential reporting of babies as live vs stillborn.

What is already known on this subject
Wide international variation exists in the reported survival of babies born at 22 to 25 weeks of gestation. An under-appreciated factor affecting these reported rates is differences in classification of whether a birth is a stillbirth or a live birth.

What this study adds
The large international variation in survival rates for births at 22-23 weeks arises in part from differences in proportion of births reported as live births, which itself is closely connected to provision of active care.
Contributors’ Statement:
Lucy K. Smith: Dr Smith conceptualized and designed the study, acquired, analyzed and interpreted data, and drafted the manuscript.
Naho Morisaki: Dr Morisaki conceptualized and designed the study, acquired, analyzed and interpreted data, and drafted the manuscript.
Nils-Halvdan Morken, Mika Gissler, Paromita Deb-Rinker, Jocelyn Rouleau, Stellan Hakansson; Dr Morken, Dr Gissler, Dr Deb-Rinker, Dr Rouleau and Dr Hakansson acquired, analyzed and interpreted data and reviewed and revised the manuscript for important intellectual content.
Michael R. Kramer, Michael S. Kramer: Dr Kramer and Dr Kramer provided administrative support, interpreted data and reviewed and revised the manuscript for important intellectual content.
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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Abstract

Objective: To explore international differences in the classification of births at 22 to 25 weeks gestation as stillbirths or live births, and its subsequent impact on calculation of survival rates.

Methods Using national data on births at 22-25 weeks gestation from the US (2014, n=11,144), Canada (2009-2014, n=5,668), the UK (2014-2015 n=2,992), Norway (2010-2014, n=409), Finland (2010-2015, n=348), Sweden (2011-2014, n=489), and Japan (2014-2015, n=2,288), we compared surviving rate to day 28 calculated for each completed week using different denominators: all births; births alive at onset of labor; live births; live births surviving to 1 hour; live births surviving to 24 hours.

Results: For babies born at 22 weeks gestation, neonatal survival rates using live births as the denominator varied from 3.7 to 56.7% among the seven countries. This variation decreased when the denominator was changed to include stillbirths, i.e., all births (1.8-22.3%) and fetuses alive at onset of labor (3.7-38.2%), or to exclude early deaths and limited to births surviving at least 12 hours (50.0-77.8%). Similar trends were seen for babies born at 23 weeks gestation. Variation in survival diminished considerably at 24 and 25 weeks gestation.

Conclusions: International variation in neonatal survival rates for births at 22-23 weeks diminished considerably when including stillbirths in the denominator, suggesting that the variation arises in part from differences in proportion of births reported as live births, which itself is closely connected to provision of active care.
Introduction

Wide international variation exists in the reported survival of babies born at 22 to 25 weeks of gestational age. Rates of neonatal survival at 22 weeks range from 0.7% reported in France\(^1\) to 2.0% in the United Kingdom (UK)\(^2\), 5.1% in the United States (US)\(^3\), 9.8% in Sweden\(^4\) and 33.1% in Japan\(^5\). This wide range persists at 23 weeks (1-52%) and 24 weeks (31-67%). Up-to-date relevant and gestation-specific survival rates are required for evidence-based counselling and decision-making.

Rysavy et al highlight the need for studies to report their results in ways that ensure comparability between populations\(^7\). However an under-appreciated factor affecting reported survival rates among periviable births is related to differences in registration as a stillbirth or a live birth, and whether a baby dies in the delivery room or survives to be admitted to a neonatal intensive care unit (NICU). These decisions may be closely related to the level of provision of obstetric and neonatal intensive care provided.\(^8\)

Standard neonatal mortality rates use the number of live births as the denominator. However, survival rates appear to increase when babies with a high survival potential are selectively classified as live births, that is, a baby may not be considered to be “live-born” unless that baby survives a certain period of time, is born with “sufficient” birth weight or gestational age, or active treatment is initiated. Wide international and regional variations have been observed in whether births at these early gestations are reported as live- or stillborn\(^13\), and shown to be related to whether obstetric interventions aiming for better infant outcomes were conducted or not.\(^9,\,10\)

Similarly, survival rates based on NICU admissions increase when babies with a high survival potential are selectively given active treatment. International guidelines vary widely
about whether to provide comfort care vs resuscitation and active treatment to births at extremely low gestations\textsuperscript{6,11}.

In this study, we explore international differences in the classification of births at 22 to 25 weeks gestation as antepartum or intrapartum stillbirths or neonatal deaths, and the subsequent impact of these differences on neonatal survival rates. We use data from 7 high-income countries, including two countries (Japan\textsuperscript{5,12} and Sweden\textsuperscript{4}) that have reported considerably higher rates of survival at periviable gestations.

**Methods**

Our study was conducted using the most recent national and population-based birth registry data available from the US, the UK, Canada, Finland, Norway, Sweden, and Japan as of January, 2017. We aimed to collect data on all stillbirths (excluding termination of pregnancies), live births and neonatal deaths for births at 22 to 25 weeks of gestation in 2014-2015. However, for countries with small populations (Norway, Finland, Sweden, Canada), we collected multiple years of data, including the most recent available. Thus the years of data included differed slightly by country: US (2014), Canada (2009-2014), UK (2014-2015), Norway (2010-2014), Finland (2010-2015), Sweden (2011-2014), and Japan (2014-2015).

Finnish, Norwegian, and Swedish data were obtained from nationwide Medical Birth Registers, and Japanese data were obtained from national vital statistics data. UK data were obtained from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK, the national UK audit of perinatal mortality. Canadian data were obtained from hospitalization records in the Discharge Abstract Database of the Canadian Institute for Health Information, which includes all hospital births in all Canadian provinces and
territories except Quebec. US data were obtained from the Natality Public Use files, which are maintained by the National Center for Health Statistics, which contains births, infant deaths and fetal deaths data registered in the 50 states, the District of Columbia, and New York City.

Gestational age was determined using an ultrasound- or clinical-based estimate, as available in each country. In the UK, Canada, Finland, Norway, Sweden and Japan, gestational age estimates were primarily based on ultrasound dating during the first or early second trimester and on last menstrual date if ultrasound dating was not available. For the US, we used the best obstetric estimate of gestation, which is recorded by the birth attendant based on all perinatal factors and assessments. In practice, this estimate is often based on ultrasound dating or, when the ultrasound estimate is unavailable, the date of the last menstrual period.

For all countries, aggregated data were obtained, with counts of births by gestational week. Timing of death was categorized as antepartum stillbirth, intrapartum stillbirth, stillbirth of unknown timing; live birth ending in a death within 1 hour of birth, 1-11 hours, 12-23 hours, 1-6 days, or 7-27 days; or live birth surviving to 28 days. The number of live-born infants who died before 12 hours was not available for the US, and the number of live-born infants who died before 1 hour and before 12 hours was not available for Norway. The Swedish and Canadian data did not report antepartum and intrapartum stillbirths separately; thus all stillbirths were classified as stillbirths of unknown timing for these countries. While registration of live births is mandatory in all countries, regardless of gestational age or birth weight, criteria for registration of stillbirths differ by country (Table 1). However, all datasets used for this study included data for all births \( \geq 22 \) weeks’ gestation, regardless of birthweight.

Statistical analysis
The overall characteristics of births at 22 to 25 weeks are described using the ratio of live births to stillbirths, and of antepartum to intrapartum stillbirths, as well as annual rates of live births at 22-25 weeks.

To explore differences in the timing of death by gestational age for births at 22-25 weeks of gestation, we first calculated the percentage of births (among all live births and stillbirths) by time of death (antepartum stillbirth, intrapartum stillbirth, or stillbirth of unknown timing; live birth with death within 1 hour, at 1-11 hours, 12-23 hours, 1-6 days, or 7-27 days; and live birth surviving 28 days) for each gestational week of birth from 22 to 25 weeks. Next, we computed survival rate until 28 days using various denominators: all births; all fetuses alive at onset of labor; all live births; births surviving to 1 hour; births surviving to 24 hours; and births surviving to 7 days) for each country and gestational week. We compared survival rates in each country with the rate in all other countries combined, with Bonferroni correction (multiple comparisons).

Reported survival rates are influenced by differences in quality of care, as well as gestation-specific decision making regarding birth registration and resuscitation practices. We therefore also calculated the mortality rate at each gestation based on the number of fetuses at risk of stillbirth or neonatal death. For example, the perinatal mortality at 22 weeks of gestation was calculated as the number of stillbirths plus neonatal deaths of infants born at 22 weeks gestation divided by the total number of live births and stillbirths occurring at or after 22 weeks. This mode of calculation is not influenced by differences in registration and classification of live births vs stillbirths, resuscitation practices, or offer or withdrawal of treatment\(^\text{13}\), provided that all births are registered at or after 22 weeks.

Using outcomes at 25 weeks as a proxy for baseline quality of care, we then calculated risk differences and 95% confidence intervals between period-specific survival rates for births at
compared to 25 weeks for each country, for each of the following time periods: during
delivery, first hour of life, 1-23 hours of life, and 1-27 days of life. Survival rates were based
on all infants surviving to the beginning of each time period.

This study only used aggregated datasets which were created and provided by researchers
with access to individual data for research purposes, and thus was exempt from ethical
review. All analyses were conducted using Stata 13 SE (Stata Corp, College Station, TX).

Results

Table 1 shows birth registrations for each country. The rate of births at 22-25 weeks
gestation was lowest in Finland (1.79 per 1000 total births) and highest in US (4.64 per 1000
total births). The pattern was similar when limited to live births, ranging from 1.16 per 1000
in Finland to 3.22 per 1000 in the US.

Classification of births

At 22 weeks, the proportion of total births reported as live-born varied widely among the 7
study countries, from 25.7% (Norway) to 53.3% (Canada) (Figure 1). The percentage of
births reported as live-born increased with advancing gestation in each country.

For those countries reporting antepartum and intrapartum stillbirths separately, the percentage
of all 22-week births reported as dying in the intrapartum period ranged from 11.9% in
Finland to 23.1% in the UK. Intrapartum stillbirths declined with advancing gestation within
countries, and so did the variation among countries. The break-down of timing of death for
deliveries alive at onset of labor is shown in eFigure 1 for these five countries.
For live births, wide variations were seen in the percentage of live-born babies at 22 weeks gestation dying before 1 hour (9.5%-41.9%). Again, these differences narrowed with increasing gestational age and nearly disappeared by 25 weeks.

Survival to 28 days of life

Figure 2 shows neonatal survival rates among the 7 different countries calculated using the different denominators. For births at 22 weeks gestation, survival to 28 days varied greatly among countries and changed substantially with the use of different denominators. Neonatal survival based on all births ranged between 1.8 and 22.3%, with Japan and Sweden having the highest rates. For fetuses alive at onset of labor, survival ranged between 3.7 and 38.2%. Variation increased for survival of live births (3.7 to 56.7%) and for live births surviving the 1st hour of life (6.0 to 62.6%). Variation declined substantially for babies surviving 12 hours (50.0 to 77.8%), 24 hours (50.0 to 79.3%) and 7 days (66.7 to 96.0%). Despite this reduced variation, substantial differences remained among countries when including stillbirths or when limited to babies surviving at least 12 hours.

Similar trends were seen for births at 23 weeks gestation. Variation in survival was highest when comparisons were based on all live births (20.0% to 79.3%) or babies surviving at least 1 hour (25.8 to 84.8%) and declined when including stillbirths or comparing babies who survived 12 hours or more; substantial differences in outcomes remained, however, among countries. Similar trends were seen at 24 and 25 weeks gestation, but the variation in survival diminished considerably.

As shown in Figure 3, mortality rates at all gestational ages from 22 to 25 weeks based on fetuses-at-risk (FAR) were lowest in Sweden, Finland and Japan and highest in the US, Canada. The ranking among countries changed substantially with use of the FAR denominator. The US had the worst rank based on FAR, while the rank for Finland improved.
The wide range in FAR-based mortality observed at 22 weeks gestation decreased with increasing gestation.

28-day survival at 22 vs 25 weeks

Differences in period survival rates for the four time periods examined (during delivery, first hour of life, 1-23 hours of life, 1-6 days of life), based on infants surviving to the beginning of each period, are shown in Figure 4. Risk differences between period-specific survival at 22 vs 25 weeks varied by country and time period of interest. The largest variation was observed at 1-23 hours, with Japan [-0.19 (95%CI -0.24, -0.14)] and Sweden [-0.23 (95%CI -0.34, -0.12)] showing much smaller differences than the other countries.

Discussion

Our findings suggest that the wide variation seen in neonatal mortality rates among periviable babies arises partly from differences in proportion of births reported as live births. International variation was diminished when including stillbirths or when limited to births surviving 12 hours or more, although some survival differences among countries remained. International variation in survival of live-born infants was at its highest at 22 weeks gestation and declined with advancing gestational age, with small differences observed at 25 weeks of gestation. Rankings changed substantially for some countries when exploring mortality based on the fetuses-at-risk approach.

For deliveries at 22 and 23 weeks, country differences in neonatal mortality rate were largest for the standard neonatal mortality rate (denominator is all live births) and when based on infants surviving the first hour (which is strongly related to resuscitation practices), and much smaller but still evident when based on all births including stillbirths. These findings highlight a “denominator bias” when reporting and interpreting the survival of periviable
births, with differences in obstetric approaches during labor as well as mis-classification of neonatal births as stillbirths influencing international, regional or even local comparisons of infant survival. This bias has been discussed previously, especially with respect to the validity of regional or institutional comparisons of infant outcomes based on babies admitted to a NICU, where admission criteria are variable among hospitals, regions and countries\textsuperscript{14}. However, we observed that even expanding the denominator from NICU admissions to all live births is insufficient.

Interestingly, in our study, the magnitude of the change in 22- and 23-week survival rates when based on different denominators was directly proportional to reported survival rates. That is, countries with higher reported survival rates (Japan and Sweden) were influenced to a larger degree than countries with lower reported survival (eFigure 2, a modified figure using the same information as included in Figure 2). Notably, Japan showed markedly better survival when the denominator was limited to births of babies alive at the onset of labor, compared to when the denominator was all births. However, while the magnitude of the country differences in survival rates fluctuated by denominator, these two countries maintained the highest survival rankings irrespective of the choice of denominator. Variation among countries in the ratio of live births to stillbirths has been reported at the international\textsuperscript{10, 15, 16}, regional\textsuperscript{17} and hospital\textsuperscript{3} level. Variations in the ratio of live births to stillbirths at very early gestations may reflect some true differences in occurrence but are also influenced by differences in perceived viability. The Models of OrganiSing Access to Intensive Care for very preterm births (MOSAIC) study, a prospective study of periviable birth in 10 regions in Europe found wide variation in the proportion of 22-23 week births alive at onset of labor admitted to the NICU (0-79.6%). Regional differences in survival were associated with provision of obstetric interventions, including administration of corticosteroids, antenatal transfer to a level-III perinatal center, and caesarean delivery for
fetal indications. The subsequent Effective Perinatal Intensive Care in Europe (EPICE) study conducted in 2011-2012 in 12 regions across Europe showed variation in proportion of 23 week births reported as stillbirths, as well as that in provision of antenatal steroids and respiratory support. If obstetric management does not aim to ensure fetal survival, periviable infants would likely die shortly after birth or even during delivery. Furthermore, some of these deaths may be differently classified as intrapartum stillbirths. Our study shows that such differences in perceived viability may strongly influence reported neonatal mortality rates by changing the ratio of live births and stillbirths at these very early gestations as seen in the UK and internationally.

In our study, while the international variation in survival rates are also greatest when based on all live births or those alive at 1 hour, excluding deaths within the first day, especially those occurring at 1-12 hours of life, reduced that variation. As infants not admitted to neonatal care most likely die during their first day, it is likely that the wide international range in survival rates largely reflects differences in neonatal management of periviable births. For deliveries at 22 weeks, first-day survival was much higher in Japan and Sweden than the other countries, both before and after taking into account survival at 25 weeks. Country rankings of first-day survival rates were similar to rankings of first-hour survival. It is likely that hospitals and countries with higher survival rates for infants born at very low gestations are more willing to resuscitate them at birth, thereby reducing their risk of death within the first hour of life.

How can such information be used? In order to counsel parents faced with a birth at the limit of viability, clinicians need to be able to access up-to-date, reliable and relevant information on survival. Survival based on denominators other than live births may also help clinicians in counselling women and their partners. Survival based on all births alive at 24 hours conveys
survival once babies have made it through the high-risk first day of life, and could be used for choosing among several neonatal intensive care units. Survival based on fetuses alive at the onset of labor could be more useful in antenatal counselling, as it incorporates the chances of babies surviving delivery.

Even such survival rates are subject to variation in clinical practice, however, likely reflecting perceptions of viability relating to local differences in religious and cultural values and legal environment. While we did not have access to information on resuscitation and treatment initiation in this study, the residual variation in international outcomes for all denominators likely reflects differences among countries in initiation of active treatment for periviable babies, and in whether and when invasive life-supporting care is withdrawn. Other variations may arise due to whether termination of pregnancy is allowed at these gestations, variation in the timing of second-trimester ultrasound scans, which can influence the gestational age at detection of some antepartum stillbirths and even the gestational age estimate of live births.

Strengths and limitations

Our study benefits from national population-based data from each country, removing the problems associated with comparing outcomes from single hospitals, networks of hospitals, or geographically limited populations. We were also able to exclude terminations of pregnancy for all participating countries. Differences in access to termination of pregnancy would certainly lead to additional variation if such terminations were included. Populations with differing access to pregnancy termination would show even larger variations in births and deaths at extremely low gestational ages.
We observed wide international variations registration of births at 22 to 25 weeks of gestation, especially for stillbirths. Although some of this variation could have arisen from differential ascertainment of stillbirths at these gestations, reporting of stillbirths was mandatory from 22 weeks in all countries participating in our study, except the UK (where it was collected via a national audit). The quality of data available for analysis highlights a reflection for many years on the management of extremely preterm babies in these countries, including published analyses of recent cohorts. Even wider variations may exist in classifying such births among other high-income countries.

Despite the benefit of national-level data, the rarity of births at very early gestations required accumulated data over a number of years. International differences in the calendar years under study from 2010 to 2015 may have affected our results, as survival has improved over time. However, the overall time period covered is only five years, with all countries contributing data for 2014.

Conclusions

In conclusion, we compare international population-based survival data using a variety of denominators from fetuses at risk, total births, fetuses alive at onset of labor, and all live births through those surviving to 7 days. Our data from a range of high-income countries should be useful for inter-country comparisons, but also for parents’ and clinicians’ decision-making at different times from early onset of labor, through to prediction of survival following admission to a neonatal unit. Most importantly, however, our findings here underline the need for caution when interpreting data on neonatal survival based on live births only from different countries.
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References


Legends

Table 1 Country characteristics of registration of births at 22-25 weeks of age

Figure 1. Percentage of births by outcome, gestational age and country of birth

Footnotes: Cells for antenatal deaths and intrapartum deaths are displayed added together for Sweden and Canada, cells for <12hr & <24 hrs are displayed added together for US, and cells for <1h & <12hr & <24hr are displayed added together for Norway, all due to lack of separated data. Cells for <7d & <28d at 22 weeks for Canada are displayed added together due to small numbers.

Figure 2. Percentage of births surviving to 28 days of life by country of birth and gestational age (weeks) based on different denominators: all births; births alive at onset of labor; livebirths; births alive at 1 hour, births alive at 12 hours, births alive at 24 hours and births alive at 7 days.

Footnotes: Data for “among births alive at onset of labor” is missing for Sweden and Canada, data for “among births alive at 1 hour” are missing for Norway, and data for “among births alive at 12 hours” is missing for US and Canada.

Figure 3. Mortality rates based on fetuses at risk by gestational age and country of birth

Figure 4. Differences in period-specific survival rates between births at 22 weeks vs 25 weeks of gestation by country of birth