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

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OBJECTIVES: To explore international differences in the classification of births at extremely low gestation and the subsequent impact on the calculation of survival rates.

METHODS: We used national data on births at 22 to 25 weeks' gestation from the United States (2014; n = 11144), Canada (2009–2014; n = 5668), the United Kingdom (2014–2015; n = 2992), Norway (2010–2014; n = 409), Finland (2010–2015; n = 348), Sweden (2011–2014; n = 489), and Japan (2014–2015; n = 2288) to compare neonatal survival rates using different denominators: all births, births alive at the onset of labor, live births, live births surviving to 1 hour, and live births surviving to 24 hours.

RESULTS: For births at 22 weeks' gestation, neonatal survival rates for which we used live births as the denominator varied from 3.7% to 56.7% among the 7 countries. This variation decreased when the denominator was changed to include stillbirths (ie, all births [1.8%–22.3%] and fetuses alive at the onset of labor [3.7%–38.2%]) or exclude early deaths and limited to births surviving at least 12 hours (50.0%–77.8%). Similar trends were seen for infants born at 23 weeks' gestation. Variation diminished considerably at 24 and 25 weeks' gestation.

CONCLUSIONS: International variation in neonatal survival rates at 22 to 23 weeks' gestation diminished considerably when including stillbirths in the denominator, revealing the variation arises in part from differences in the proportion of births reported as live births, which itself is closely connected to the provision of active care.

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WHAT'S KNOWN ON THIS SUBJECT: Wide

international variation exists in the reported survival of infants born at 22 to 25 weeks' gestation. An underappreciated factor affecting these reported rates is differences in the classification of whether a birth is a stillbirth or live birth.

WHAT THIS STUDY ADDS: The large international variation in survival rates for births at 22 to 23 weeks' gestation arises in part from differences in the proportion of births reported as live births, which itself is closely connected to the provision of active care.

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Wide international variation exists in the reported survival of infants born at 22 to 25 weeks' gestational age. Rates of neonatal survival at 22 weeks' gestation range from 0.7% in France¹ to 2.0% in the United Kingdom,² 5.1% in the United States,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%) gestation.⁶ Up-to-date relevant and gestationspecific survival rates are required for evidence-based counseling and decision-making.

Rysavy et al⁷ highlight the need for researchers to report their results in ways that ensure comparability among populations. However, an underappreciated factor affecting reported survival rates among periviable births is related to differences in registration as a stillbirth or a live birth and whether an infant dies in the delivery room or survives to be admitted to a NICU. These decisions may be closely related to the level of provision of obstetric and neonatal intensive care provided.⁸

Standard neonatal mortality rates include the number of live births as the denominator. However, survival rates appear to increase when infants with a high survival potential are selectively classified as live births; that is, an infant may not be considered to be "live born" unless that infant 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 gestational ages are reported as live or stillborn⁹ and are shown to be related to whether obstetric interventions for better infant outcomes were conducted or not.^{10,11}

Similarly, survival rates based on NICU admissions increase when infants with a high survival potential are selectively given active treatment. International guidelines vary widely about whether to provide comfort care versus resuscitation and active treatment to births at extremely low gestational ages.^{6,12}

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 2 countries (Japan^{5,13} and Sweden⁴) that have reported considerably higher rates of survival at periviable gestational ages.

METHODS

Our study was conducted using the most recent national and populationbased birth registry data available from the United States, the United Kingdom, 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' gestation from 2014 to 2015. However, for countries with small populations (Norway, Finland, Sweden, and Canada), we collected multiple years of data, including the most recent available. Thus, the years of data included differed slightly by country: United States (2014), Canada (2009–2014), United Kingdom (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. United Kingdom data were obtained from the Mothers and Babies: Reducing Risk Through Audits and Confidential Inquiries Across the United Kingdom program, the national United Kingdom 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. United States data were obtained from the Natality Public Use files, which are maintained by the National Center for Health Statistics, which contains data on births, infant deaths, and fetal deaths registered in the 50 states (including the District of Columbia) and New York City.

Gestational age was determined by using an ultrasound- or clinical-based estimate as available in each country. In the United Kingdom, Canada, Finland, Norway, Sweden, and Japan, gestational age estimates were primarily based on ultrasound dating during the first or early-second trimester and on the last menstrual date if ultrasound dating was not available. For the United States, we used the best obstetric estimate of gestation, which is recorded by the birth attendant and is 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, or stillbirth of unknown timing; live birth ending in a death within 1 hour of birth, 1 to 11 hours of birth, 12 to 23 hours of birth, 1 to 6 days of birth, or 7 to 27 days of birth; or live birth surviving to 28 days. The number of live-born infants who died before 12 hours was not available for the United States, and the number of live-born infants who died before 1 hour and before 12 hours was not available for Norway. Antepartum and intrapartum stillbirths were not displayed separately in Swedish and Canadian data; thus, all stillbirths

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Country, y	United States	Canada	United Kingdom	Norway	Finland	Sweden	Japan
Stillbirth registration criteria	≥20 wk or ≥350 gª	≥20 wk or ≥500 g	≥22 wk ^b	≥12 wk	≥22 wk or ≥500 g	≥22 wk	≥12 wk
Birth at 22–25 wk per 1000 births ^c	4.64 (18645/4014710)	3.26 (5668/1 736 472)	3.19 (4879/1 528 807)	2.18 (662/303 945)	1.79 (633/353 572)	2.27 (1034/353572)	2.21 (4592/2079409)
Live birth at 22–25 wk per 1000 births ^d	3.22 (12861/3993873)	2.30 (3979/1 728 441)	2.02 (3069/1 521 500)	1.32 (400/302 826)	1.16 (410/352579)	1.55 (705/453 445)	1.31 (2714/2073181)

All numbers include births with missing gestational age at delivery in the denominator.

^a Registration criteria differ by state, with states using \geq 20 wk, \geq 350 g, or a combination of the 2.

^b National registration is for births at ≥24 wk. Additional reporting of all deaths from ≥22 wk are included in the data.

 $^{\rm c}$ Total births at 22–25 wk per total births at ≥22 wk.

^d Live births at 22–25 wk per live births at \geq 22 wk.

were classified as stillbirths of unknown timing for these countries. Although the registration of live births is mandatory in all countries regardless of gestational age or birth weight, criteria for the registration of stillbirths differ by country (Table 1). However, all data sets used in this study included data for all births at \geq 22 weeks' gestation regardless of birth weight.

The overall characteristics of births at 22 to 25 weeks' gestation are described by using the ratio of live births to stillbirths, of antepartum to intrapartum stillbirths, as well as the annual rates of live births at 22 to 25 weeks' gestation.

To explore differences in the timing of death by gestational age for births at 22 to 25 weeks' 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 birth from 22 to 25 weeks' gestation. Next, we computed the survival rate until 28 days using various denominators (all births, all fetuses alive at the 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 age. We

compared the survival rates in each country with the rate in all the other countries combined with Bonferroni correction (multiple comparisons).

Reported survival rates are influenced by differences in the quality of care as well as gestationspecific decision-making regarding birth registration and resuscitation practices. Therefore, we also calculated the mortality rate at each gestation based on the number of fetuses at risk (FARs) for stillbirth or neonatal death. For example, the perinatal mortality at 22 weeks' gestation was calculated as the number of stillbirths plus the number of 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' gestation. This mode of calculation is not influenced by differences in the registration and classification of live births versus stillbirths, resuscitation practices, or offer or withdrawal of treatment,9 provided that all births are registered at or after 22 weeks' gestation.

Using outcomes at 25 weeks' gestation as a proxy for baseline quality of care, we then calculated risk differences and 95% confidence intervals (CIs) between periodspecific survival rates for births at 22 compared with 25 weeks' gestation for each country for each of the following time periods: during delivery, during the first hour of life, from 1 to 23 hours of life, and from 1 to 27 days of life. Survival rates were based on all infants surviving to the beginning of each time period.

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

RESULTS

Table 1 shows birth registrations for each country. The rate of births at 22 to 25 weeks' gestation was lowest in Finland (1.79 per 1000 total births) and highest in the United States (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 United States.

Classification of Births

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



FIGURE 1

Percentage of births by outcome, gestational age, and country of birth. Cells for antenatal deaths and intrapartum deaths are displayed added together for Sweden and Canada; cells for <12 and <24 hours are displayed added together for the United States; and cells for <1, <12, and <24 hours are displayed added together for Norway, all because of a lack of separated data. Cells for <7 and <28 days at 22 weeks' gestation for Canada are displayed added together because of small numbers.

For those countries reporting antepartum and intrapartum stillbirths separately, the percentage of all births at 22 weeks' gestation reported as dying in the intrapartum period ranged from 11.9% in Finland to 23.1% in the United Kingdom. Intrapartum stillbirths declined with advancing gestation within countries, and so did the variation among countries. The breakdown of the timing of death for deliveries alive at the onset of labor is shown in Supplemental Fig 5 for these 5 countries. For live births, wide variations were seen in the percentage of live-born infants 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' gestation.

Survival to 28 Days of Life

Figure 2 shows neonatal survival rates among the 7 different countries calculated by 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 the onset of labor, survival ranged between 3.7% and 38.2%. Variation increased for survival of live births (3.7%–56.7%) and for live births surviving the first hour of life (6.0%–62.6%). Variation declined substantially for infants surviving 12 hours (50.0%–77.8%), 24 hours (50.0%-79.3%), and 7 days (66.7%–96.0%). Despite this reduced variation, substantial differences remained among countries when including stillbirths or when limited to infants 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%–79.3%) or infants surviving at least 1 hour (25.8%– 84.8%) and declined when including stillbirths or comparing infants who survived ≥12 hours; however, substantial differences in outcomes remained among countries. Similar trends were seen at 24 and 25 weeks' gestation, but the variation in survival diminished considerably.

As shown in Fig 3, mortality rates at all gestational ages from 22 to 25 weeks' gestation based on the number of FARs were lowest in Sweden, Finland, and Japan and highest in the United States and Canada. The ranking among countries changed substantially with the use of the FARs denominator. The United States had the worst rank on the basis of the number of FARs, whereas the rank for Finland improved. The wide range in mortality based on the number of FARs observed at 22 weeks' gestation decreased with increasing gestation.

Twenty-Eight–Day Survival at 22 vs 25 Weeks' Gestation

Differences in period survival rates for the 4 time periods examined



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 the onset of labor, live births, births alive at 1 hour, births alive at 12 hours, births alive at 24 hours, and births alive at 7 days. Data for among births alive at the onset of labor are 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 are missing for the United States and Canada.



(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 Fig 4. Risk differences between period-specific survival at 22 vs 25 weeks' gestation varied by country and time period of interest. The largest variation was observed at 1 to 23 hours, with Japan (-0.19; 95% CI -0.24 to -0.14) and Sweden (-0.23; 95% CI -0.34 to -0.12) showing much smaller differences than the other countries.

DISCUSSION

Our findings reveal that the wide variation seen in neonatal mortality rates among periviable infants arises partly from differences in the proportion of births reported as

FIGURE 3

Mortality rates based on the number of FARs by gestational age and country of birth.



FIGURE 4

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

live births. International variation was diminished when including stillbirths or when limited to births surviving ≥12 hours, although some survival differences among countries remained. International variation in the survival of liveborn infants was at its highest at 22 weeks' gestation and declined with advancing gestational age, with small differences observed at 25 weeks' gestation. Rankings changed substantially for some countries when exploring mortality based on the FARs approach.

For deliveries at 22 and 23 weeks' gestation, 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 this was much smaller but still evident when based on all births, including stillbirths. These findings reveal a "denominator bias" when reporting and interpreting the survival of periviable births, with differences in obstetric approaches during labor as well as the misclassification of neonatal births as stillbirths influencing international, regional, and 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 infants admitted to a NICU, in which admission criteria vary among hospitals, regions, and countries.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 survival rates at 22 and 23 weeks' gestation 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 (Supplemental Fig 6, a modified figure using the same information is included in Fig 2). Notably, Japan showed markedly better survival when the denominator was limited to births of infants alive at the onset of labor compared with when the denominator was all births. However, although the magnitude of the country differences in survival rates fluctuated by denominator, these 2 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,^{10,15,16} regional,¹⁷ and hospital³ levels. Variations in the ratio of live births to stillbirths at early gestational ages may reflect some true differences in occurrence but are also influenced by differences in perceived viability. Researchers in the Models of Organizing Access to Intensive Care for Very Preterm Births study, a prospective study of periviable births in 10 regions in Europe, found wide variation in the proportion of births at 22 to 23 weeks' gestation alive at the onset of labor admitted to the NICU (0%–79.6%). Regional differences in survival were associated with the provision of obstetric interventions, including the administration of corticosteroids, antenatal transfer to a level III perinatal center, and cesarean delivery for fetal indications.^{9,15} The subsequent Effective Perinatal Intensive Care in Europe study conducted from 2011 to 2012 in 12 regions across Europe revealed variation in the proportion of births at 23 weeks' gestation reported as stillbirths as well as that in the provision of antenatal steroids and respiratory support.^{10,18} 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.^{15,19,20} Our study reveals that such differences in perceived viability may strongly influence reported neonatal mortality rates by changing the ratio of live births and stillbirths at these early gestational ages, as seen in the United Kingdom¹⁷ and internationally.¹⁶

In our study, although 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 to 12 hours of life, reduced that variation. Because 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' gestation, first-day survival was much higher in Japan and Sweden than in the other countries, both before and after taking into account survival at 25 weeks' gestation. 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 low gestational ages 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? 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 counseling women and their partners. Survival based on all births alive at 24 hours conveys survival once infants have made it through the high-risk first day of life and could be used for choosing among several NICUs. Survival based on fetuses alive at the onset of labor could be more useful in antenatal counseling because it incorporates the chances of infants 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

environments. Although 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 the initiation of active treatment of periviable infants and in whether and when invasive life-supporting care is withdrawn. Other variations may arise because of whether the termination of a pregnancy is allowed at these gestational ages and 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.

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 services would certainly lead to additional variation if such terminations were included. Populations with differing access to pregnancy termination services would show even larger variations in births and deaths at extremely low gestational ages.

We observed wide international variations in the registration of births at 22 to 25 weeks' gestation, especially for stillbirths. Although some of this variation could have arisen from differences in underreporting rates of stillbirths at these gestational ages, reporting of stillbirths was mandatory from 22 weeks' gestation in all countries participating in our study except the United Kingdom (where it was collected via a national audit). We believe the quality of the data available for our analysis is ensured by the high quality of the

management of extremely preterm infants maintained for many years in these countries, as is demonstrated through the publications on recent cohorts. Even wider variations may exist among other highincome countries where stillbirth registration is not yet mandatory, and where care of extremely preterm infants is not as of high quality.

Despite the benefit of nationallevel data, the rarity of births at early gestational ages 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 because survival has improved over time.^{2,21–24} However, the overall time period covered is only 5 years, with all countries contributing data for 2014.

CONCLUSIONS

We compare international population-based survival data using a variety of denominators, including the number of FARs, total births, fetuses alive at the 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 not only for intercountry comparisons but also for parents' and clinicians' decision-making at different times, from early onset of labor to the prediction of survival after admission to a neonatal unit. Most importantly, however, we underline the need for caution when interpreting data on neonatal survival based on live births only from different countries.

ABBREVIATIONS

CI: confidence interval FAR: fetus at risk

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