Title: Classification of causes and associated conditions for stillbirths and neonatal deaths

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The International Stillbirth Alliance Collaborative for Improving Classification of Perinatal Deaths¥

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Abstract

Introduction

Accurate and consistent classification of causes and associated conditions for perinatal deaths is essential to inform strategies to reduce the five million which occur globally each year. With the majority of deaths occurring in low and middle income countries (LMICs), their needs must be prioritised. The aim of this paper is to provide an overview of the challenges of classification of perinatal death, the contemporary classification systems including the WHO ICD-Perinatal Mortality (ICD-PM), and next steps.

Findings

Over the period from 2009 to 2014, 81 new or modified classification systems were identified with the majority developed in high income countries (HICs). Structure, definitions and rules and therefore data on causes vary widely and implementation is suboptimal. While system testing is limited, none appear ideal. Several systems result in a high proportion of unexplained stillbirths, prompting HICs to use more detailed systems that require data unavailable in LICs. Some systems appear to perform well across these different settings. ICD-PM addresses some shortcomings of ICD-10 for perinatal deaths, however important limitations remain, particularly for stillbirths.

Conclusions

A global approach to classification is needed and seems feasible. The new ICD-PM system is an important step forward and improvements will be enhanced by wide scale use and evaluation. Implementation requires national level support and dedicated resources. Future research should focus on implementation strategies and evaluation methods, defining placental pathologies, and ways to engage parents in the process.

Keywords

Classification, causes of death, global, ICD, stillbirth, neonatal death, perinatal death.

Introduction

With over five million perinatal deaths globally each year and slow progress in reducing these deaths, prevention must be prioritised[1, 2]**.** In 1986 Whitfield[3] stated that the goal of classification of perinatal deaths was 'to identify deficiencies in the provision of care, to focus attention where improvements are already possible and to indicate where new developments or knowledge may be expected to lead to further advances'. Accurate and consistent classification of causes, associated conditions, and other contributing factors (e.g. substandard care) is the cornerstone of prevention, enabling high quality benchmarking and ongoing monitoring to inform policy, practice and research. Achieving these goals requires optimal diagnostic testing and multidisciplinary review as part of high quality perinatal mortality audit. Perinatal death is a tragedy for parents and families[4] who need information to understand what caused their baby's death, and whether the cause is likely to recur[5, 6]. Therefore, in addition to informing prevention efforts at the population level, establishing an accurate cause of death is necessary for parents to understand why their baby died, support them to cope with the death of their baby, and to inform care in future pregnancies with the hope of reducing further perinatal deaths in this high-risk population.

Box. Purpose of audit and classification of perinatal deaths

1) To reduce deaths by enabling benchmarking and monitoring of causes of death to inform policy, practice and research;
2) To help parents understand why the death occurred; and
3) To assist both parents and their care providers in care and decision-making in subsequent pregnancies.

The utility of classification systems lies in the extent to which useful information is conserved[7]. Suboptimal systems exclude important information and result in a high proportion of deaths being classified incorrectly as "unexplained", hampering efforts to achieve the goals of classification stated above[8]. Despite decades of work, the ideal system remains elusive[9]. With 98% of perinatal deaths occurring in LMICs[10], a classification system relevant to these settings is vital.

The Lancet's Stillbirth Series in 2011 and 2016 called for the creation of a "universal classification system" for causes of stillbirth[11, 12], and the Every Newborn Action Plan (ENAP)[13] - endorsed by the United Nations - identified cause of death as a key gap in the data. ENAP proposes registration of all perinatal deaths together with identification of cause of death as a global indicator[13]. As causes vary substantially by country and setting[8], it may be difficult to accommodate the needs of all in one system, and the needs of LMICs must be prioritised due to their high burden. However, patterns of causes across HICs provide insights into prevention strategies in LMIC. Within LMIC, there are often very significant inequalities in availability and quality of care, hampering capacity to identify and classify causes of death. Therefore, an ideal system is one that can be implemented and drives clinical practice across diverse settings[14]. With an increasing focus on the need for a global approach[2, 12, 15, 16], the new WHO Application of ICD-10 to Perinatal Deaths: ICD-Perinatal Mortality (ICD-PM) is an important step forward. However, it is acknowledged that ICD-PM requires enhancements[17] and is yet to be implemented widely and evaluated.

This eighth paper of the Stillbirth and Neonatal Death Series provides an overview of the challenges in identifying a cause of perinatal death, details of and experience with contemporary systems, features of the ICD-PM system, and discusses how to operationalise a system to inform next steps in global classification.

Challenges in identifying a cause of death

Although the need for a generally accepted classification system for stillbirths and neonatal deaths is clear, it has been extremely difficult to reach consensus. In large part, this has been due to challenges with ascertaining a 'true' cause of death in many cases of stillbirth in HICs; the origin of most systems. Firstly, it can be hard to define a proximate reason for the death in part because the moment of death in stillbirths are usually not actually observed. Secondly, more than one condition potentially associated with the death may be present. If stillbirth is associated with group B streptococcal pneumonia in an infant with trisomy 18, is the death due to infection or genetic abnormality? Thirdly, association between a condition and stillbirth does not imply causation. Many conditions are risk factors rather than causes of stillbirth (e.g., smoking, advanced maternal age, obesity). Although these conditions are associated with increased risk of perinatal death, they are present in very large numbers of women with uncomplicated livebirths. Further, particular conditions may be a cause or contributor to the death in some circumstances, but not others. Chronic hypertension serves as an illustration. If chronic hypertension is severe with evidence of placental insufficiency, it may be a proximate cause of stillbirth. However, if the condition is well controlled, the baby is normally grown, and there is normal amniotic fluid volume, then chronic hypertension may be unrelated to the death.

Another major challenge is the requirement for information about associated maternal, fetal, and placental conditions which require extensive evaluation that may not be possible, especially in low resource settings[8]. Genetic testing such as microarray or karyotype, perinatal autopsy, and placental examination are expensive and not widely available outside HICs. A recent review by Heazell and Fenton showed perinatal autopsy rates of 5% in LIC compared with up to 60% in HIC[18]. In contrast, systems that do not require such data may be too simplistic to provide optimal stratification and information in HICs. A lack of a gold standard for determining an underlying cause of death, defined as the first event in the chain of events resulting in death, is another major hurdle. Many investigators use the percentage of stillbirths with identified underlying causes as a way to evaluate the utility of the system. There is no doubt that being able to assign an underlying cause of death in a majority of cases is desirable. However, it is unhelpful if the cause of death assigned is not accurate. Placental abnormalities serve to underscore this problem. Some systems allocate a cause of death based on abnormal placental histology[19, 20]. Such systems identify a cause of death in a large proportion of cases (up to 65%), but many placental abnormalities are non-specific and are present in a large percentage of livebirths[21]. Thus, in some cases, the cause of death assigned by these classification systems may be incorrect. The topic of optimal investigations to identify causes of perinatal deaths is addressed in paper seven of this series.

Contemporary classification systems

A review of classification systems for causes of perinatal deaths found 81 systems in use in the period 2009-2014, with an average of ten systems created/modified each year[22]. Systems had widely varying characteristics[22]. Classification remains an overwhelmingly HIC exercise, with 65% of systems developed, and 68% used exclusively in HICs. At the time of this review, there were no reports of any system in use in China and India - the two highest-burden countries (in terms of number of stillbirths) – however, India has recently adopted the Codac (Causes of Death and Associated Conditions) system[23]. A recent Delphi study reported 17 system characteristics of a quality global system according to expert consensus[14] (see Appendix). Six of these reached almost complete agreement amongst experts. These are, that "a global system must be": 1) easy to use, and produce data that are easily understood and valued by users; 2) have clear guidelines for use and definitions for all terms used; use rules to ensure valid assignment of cause of death categories; 3) be able to work with all levels of data (from both low-income and high-income countries), 4) including minimal levels; 5) ensure cause of death categories are relevant in all settings; and 6) produce data that can be used to inform strategies to prevent perinatal deaths. In an evaluation of the contemporary systems, none met all these features[9]. Overall, 82% of systems met fewer than five of the 17 characteristics. The most-aligned system (Codac) was aligned with just nine characteristics overall[23]. The seven most-aligned systems were Codac[23], Tulip[19], Child Health Epidemiology Reference Group (CHERG) (neonatal only)[24], Cole 1986[25], Perinatal Society of Australia and New Zealand – Perinatal Death Classification (PSANZ-PDC)[26], Kotecha 2014[27], and Ujwala 2012[28] (see Appendix). Just two of these systems were intended for use with verbal autopsy (VA). VA includes a structured interview conducted with family members or caregivers and was initially developed for regions where the majority of deaths occur outside the health care system. VA may be the single source of information in resource poor settings[28, 29]. Because VA was only recently adopted for use with stillbirth, further research to refine this tool is needed.

Another important characteristic is consistency; high inter-and intra-rater reliability. While robust data to assess agreement are limited, room for improvement is clearly evident[22]. An important feature (identified in the Delphi study and supported by WHO[30]) is the ability to include both stillbirths and neonatal deaths, as factors leading to these deaths often overlap e.g. intrapartum asphyxia, placental abruption[31]. Some contemporary systems reflect these overlapping causes, by using one list of conditions that apply to both stillbirths and neonatal deaths (e.g. the underlying cause of a neonatal death to be coded as caused by a common cause of antepartum deaths)[23]. Others accommodate stillbirths and neonatal deaths by combining two separate lists of conditions, an obstetric antecedent for stillbirths and neonatal deaths and a neonatal system to identify a "final cause of neonatal death"[26, 32, 33], which can be cumbersome. Recently developed systems in HICs, have more detailed categories and a greater focus on placental pathology[19, 20, 23, 34].

An important feature for a global system is alignment with ICD. A number of systems aim to follow ICD rules to identify a single cause, whilst allowing associated conditions to be coded[23, 26, 34]. Other systems use a more pragmatic approach for example ReCoDe (Relevant Condition at Death)[35] was developed to better understand the clinically relevant conditions for stillbirths regardless of whether an underlying cause was established. ReCoDe aimed to address the high proportion of stillbirths classified as unexplained using the Wigglesworth classification system.[36] The system resulted in a lower proportion of stillbirths coded as 'unexplained' with a shift to a higher proportion classified as 'fetal growth restriction'.

Experience with classification systems

In a systematic review of causes of stillbirth globally published 2009 to 2014, 54% of reports (33 of 61) used alternate systems to ICD. A total of 11 different non-ICD systems were used (16 reports did not state the system used)[37]. The proportion of non-ICD system use was slightly higher for HICs compared with LMICs: 18 of 28 (64%) versus 15 of 33 (45%) respectively[37] The use of disparate systems results in wide variation in reported causes of stillbirths[8, 37,12] with unexplained stillbirth ranging from 5% to 75%[37]. Reports using ICD had on average higher proportions of unexplained stillbirths. Experience with some of the commonly used ICD alternative systems is provided here to inform future steps towards a successful global system.

Experience in LMICs

Beyond research, classification of cause of stillbirth presents many challenges in low-resource settings. A substantial proportion of births occur at home without a skilled birth attendant and antenatal care includes only basic services[38]. Gestational age is generally unknown and birth weights are not routinely taken for stillborn infants. Systems that perform well in HIC may not perform as well in LMICs as data sources are quite different due to lack of laboratory service (Figure 1). To address these issues, numerous studies have attempted to ascertain cause of stillbirth using various methodologies[39]. A limitation of VA is that it relies solely on observation, without access to test results or medical records. Other disadvantages of VA are the time it takes, and the lack of reliability[40].

In LMIC settings, systems with few main categories with sub-categories that can incorporate more detailed information from other testing hold promise. One example is shown in the use of Codac in India as a national surveillance tool that has sparked several recent research reports of use in different settings with highly variable data availability[41, 42]. The key experience was that the system's utility is not diminished in populations with high levels of poverty and limited resources available for post mortem investigations. The proportion of cases classified as having an unknown cause was no higher than that reported in HIC with sophisticated testing and analyses, ranging in India from 8% (facility-based case review)[43] to 23% (tertiary facility audit)[44] and 25% (community-based VA), the latter showing 93% agreement with ICD-10 on the primary categories of causes of death (kappa: 0.90)[41]. This may reflect that causes of perinatal deaths resulting from overt and untreated pathology, are more easily observed in settings with high burden and low resources. Causes such as obstructed labour, central nervous systems malformations, and severe maternal hypertension are often large contributors to perinatal deaths in a LMIC setting and easily captured by VA[41]. Likewise, the ability to collect data on both causes and associated conditions may be more readily useful in LMIC where significant risk factors are highly prevalent and amenable to preventive efforts. In these settings, classifying associated factors with an underlying cause as 'unexplained/unknown without adequate investigation' may be most helpful by holding true to the principles of underlying cause classification while acknowledging the need for better data. There has also been success with versions of the CHERG system (for neonatal deaths only), including one without hierarchy [45] and one with hierarchy [24]. Their simplicity, with 8 and 7 causes, respectively, and no sub-categories or associated conditions, facilitates categorization of causes at a population level. It is also possible to map the results of multiple other, more complicated systems onto the CHERG categories and has been used for global reporting.

A hierarchical approach to classifying perinatal deaths, uses a structure where conditions placed higher up the hierarchy take precedence[8]. It has been proposed that this increases accuracy and ease of use and may be of particular value in low resource settings with lack of skilled personnel[46]. However, a strictly hierarchical system may not be ideal due to the complex nature of many perinatal deaths and where rules to define the hierarchy lack sound rationale. ReCoDe (RElevant COndition at DEath)[35], used in some centers in LMICs[47] and in the UK, uses a hierarchical approach to identify relevant associated conditions for stillbirth (as opposed to underlying causes) thereby reducing the need for laboratory investigations. This system results in a high proportion of stillbirths classified as 'fetal growth restriction' due to the high placement of this category in the hierarchy[8]. ReCoDe use has helped to focus the health service on preventative strategies[48]. Experience with ReCode has fed into considerations of a global system, which classified maternal and fetal/neonatal conditions side by side with conditions linked to diagnostic categories mapped to ICD[46] – a concept integrated into the WHO ICD-PM system (see below).

Another effort that builds upon the WHO ICD-PM system is the Global Network research stillbirth classification study[49], which uses a hierarchal algorithm to assign cause, based on prospectively defined rules. However, this system still needs further validation. Other systems are intended for use without a strict hierarchical approach, but retain a hierarchical structure for use only when detailed information or knowledge is too limited for detailed coding[23]. No consensus has been reached regarding whether a global classification system should be hierarchical[14], and further research is needed on the relative merits of hierarchical systems.
Systems that also include a focus on audit of substandard care in addition to classifying causes, such as the Perinatal Problem Identification Programme (PPIP)[33], may serve to address prevention more comprehensively. PPIP was introduced in South Africa as an audit tool intended to improve the quality of care in maternity units. It now covers around three quarters of births in the public sector. In sites where it was implemented well, a reduction in mortality rates of up to 30% was shown. Conversely, where implementation was poor there was either no change in mortality rates, or there was an increase [50]. PPIP is a very simple

system, and audits are generally well implemented. The main problem is completing the audit cycle; that is, altering the behaviour of clinicians and managers to achieve the necessary practice change. Another example is the *Beyond the Numbers* program in Moldova involving a comprehensive perinatal audit program. Using ReCoDe[35], combined with a substandard care audit methodology, this program was associated with a reduction in term perinatal deaths[51].

Experience in high-income countries

United Kingdom – stillbirths and neonatal deaths

In 2013 national perinatal surveillance in the UK was taken over by MBRRACE-UK (Mothers and Babies: Reducing Risk by Audit and Confidential Enquiries)[52]. In order to establish which classification of death system was going to be used a Death Classification Expert Group was convened, which reviewed available classification systems and selected the Codac system[23]. It was felt that this system would provide a greater understanding of the factors associated with antepartum stillbirth and offered the potential to give insight into opportunities where different clinical management may have led to a different outcome. In addition, Codac records sufficient detail about cause of death for serious congenital anomalies (CAs) allowing for this group to be excluded from analyses when appropriate. The system was implemented using the MBRRACE-UK online reporting system with data entered by local reporters within the Hospital Trusts and Health Boards aided by a help facility populated from the Codac website. However, Codac is a complex coding system and early review of data identified that training and guidance were required to help with use at local level.

As with other cause of death classification systems, Codac allocated a large proportion of stillbirths to the category ‘unknown’: 47% in 2013 and 46% in 2014[53, 54]. However, only 13% were actually unknown after adequate investigation[53, 54]. Despite the fact that Codac was focussed on attributing the cause of death for stillbirths, it was still able to identify a cause for a high proportion of neonatal deaths. The proportion of neonatal deaths allocated an unknown or missing cause of death was less than 10% with just under half (44%) allocated a neonatal primary cause and all but 19 neonatal deaths (1%) categorised to a clearly defined Codac sub-category[54]. The coding of deaths due to CA was a particular issue for MBRRACE-UK given the need to be able to exclude these deaths where appropriate. Guidance for coding the primary cause of death using Codac indicates that conditions should have significant lethality (5% or more) and, where there are two equally significant conditions, the first to occur would be the one coded as the primary cause of death. As such in most situations where there is a major CA this would be coded as the primary cause. However, in the MBRRACE-UK data in cases where a CA was included as an associated condition the primary cause of death was inappropriately classified as either 'fetal' or 'neonatal' within the main Codac system. Upon investigation it was unclear whether this was an informed decision or simply reflected a lack of experience with the system. To help address this and other coding issues a consultation group was established to develop training materials and advice for reporters. In addition, a frequently asked questions (FAQs) section has been added to the MBRRACE-UK online system with detailed example cases.

Prior to MMBRACE, national reports used the Wigglesworth classification system and consistently resulted in about two thirds of stillbirths being reported as 'unexplained[55]. The ReCoDe system was developed in 2005[35] to address this problem. By highlighting the frequent association between stillbirth and antecedent fetal growth restriction as mentioned above, the system "explains" a higher proportion of deaths. ReCoDe is easy to use with guidelines and definitions made available on line and has been taken up by a number of NHS centres for unit-based audit. However, its inherent simplicity was also a limitation.

Australia and New Zealand (ANZ) – stillbirths and neonatal deaths

Since the mid-1980s clinicians in Australia and New Zealand have been considering ways to classify perinatal deaths. Following initial use of a number of variations of Whitfield classification, consensus was reached for a bi-national system in 2000[56]. The PSANZ-PDC system is widely accepted and is used in both countries to report national perinatal death data. The system uses an obstetric antecedent classification for stillbirths and neonatal deaths and, in addition, a neonatal classification is used to identify a “final cause for neonatal death”. The PSANZ system also allows three associated conditions to be listed, along with the primary cause of death. Terminations of pregnancy are identifiable for each death in addition to the reason for the termination. The system results in around 20-30% of stillbirths coded as unexplained[57]. Coding as ‘other’ conditions is limited through a fairly detailed list of conditions and by including this category under each major category. The proportion of perinatal deaths assigned as due to CA is relatively high (25%). This may be due to the hierarchical approach for this category, whereby deaths in which a major CA was present are classified into this category regardless of the associated risk of death (a rule that has been removed from the most recent revision of the system). In this 3rd revision the following changes will be made: (1) additional categories to identify placental pathology; (2) a refined definition of ‘unexplained’ to exclude significant placental pathology and to identify where investigation was insufficient; and (3) improved capability to differentiate causes from associated conditions (e.g. by moving the fetal growth restriction category to the list of associated conditions rather than the list of causes). Owing to limited research, development of definitions for the new placental pathology category is proving challenging. Further, the requirement to identify a single cause of death is particularly problematic when multiple significant placental pathologies are present. Some variation in reported causes is evident across regions and definitions and rules are being revised to enhance consistency. An educational program is also provided[58].

Sweden – stillbirth only

Since 1998, all cases of stillbirth with gestational age ≥ 22+ 0 weeks in the major Stockholm area are reviewed in a perinatal audit and registered in a database. The Stockholm classification system identifies a single underlying cause of death, but it also illustrates associated factors that may have contributed. The classification consists of 17 groups. Most of the groups are subdivided into definite, probable and possible association to death. One problem has been defining criteria for diagnostic settings. Some diagnostic groups were especially hard to define, a notable example being the placental insufficiency/Intrauterine Growth Restriction Group (IUGR) group. Placental insufficiency implies any situation or condition resulting in considerable impairment of placental function, irrespective of aetiology. IUGR refers to fetuses that have failed to reach their perceived growth potential. It is overlapping with, but not equivalent to, small for gestational age, defined as fetal or birthweight below the 10th percentile, or as in Sweden two standard deviations of the gestational-age-related weight. Despite these limitations, both are included in the same diagnostic group, in order to ensure a better overview of the spectrum of entities affecting placental function and fetal growth. Importantly, this classification system does not include neonatal death, cooperation with an experienced perinatal pathologist is fundamental, and all cases are reviewed in a perinatal audit. From 2017, all births in Sweden will be reported for inclusion in this national system. The register also enables collection on causes of fetal deaths (using the Stockholm system), whether or not placental examination and autopsy was performed, and results of chromosomal testing.

The Netherlands – stillbirth and neonatal deaths

The main purpose of the TULIP classification system[59] was to use unequivocal categories of similar level, and make a distinction between underlying cause, mechanism (e.g. organ failure) - and origin of the mechanism - in order to define straightforward pathways to death. TULIP has been used in the program for nationwide Perinatal Audit alongside Wigglesworth[36] and ReCoDe[35].[35] . After four years of use in auditing over 1000 cases of perinatal death, TULIP was replaced with ReCoDe because the conditions included in the latter were more understandable to clinicians. However, with categories like asphyxia, or fetal growth restriction, and placental insufficiency at the same level, ReCoDe results were not useful in defining the groups of pathology to clearly focus upon. With a change to a national focus on perinatal deaths due to perinatal asphyxia, ReCoDe was abandoned, however, together with TULIP ReCoDe continues to be used to classify all perinatal deaths in a number of hospitals.

United States – stillbirth research

INCODE is a stillbirth classification system developed by the investigators of the Stillbirth Collaborative Research Network (SCRN)[20]. This Network conducted a multi-centre case-control study of stillbirths and live births in the US in five diverse regions. The classification system is intended for use in high resource settings because it is dependent upon more detailed data and thorough evaluation of stillbirths. The system was developed using rigorous definitions and the best evidence for assigning a cause of death. In effect, the goal was to only identify a cause of death with some certainty rather than trying to determine a cause of death in as many cases as possible. A unique feature of INCODE is the designation of level of certainty for each potential cause of death. For each cause of stillbirth, the etiology is coded as a “probable cause of death,” a “possible cause of death,” or “condition present.” This stratification allows for determination of the level of confidence regarding the cause of stillbirth. Diabetes serves as a good example. If there is stillbirth associated with diabetic embryopathy or a critically ill mother with diabetic ketoacidosis, then diabetes is considered to be a “probable” cause of death. If there is poorly controlled diabetes with a macrosomic fetus, then diabetes is considered to be a “possible” cause of death. However, if the mother has well-controlled diabetes and the fetus is normally grown, then diabetes is considered “condition present.” In a cohort of over 500 stillbirths, a probable cause was identified in 61% and a possible or probable cause in 76%[60]. INCODE also has been used successfully in other data rich cohorts[61]. However, it may not be an optimal system in cases without extensive data and evaluation. There are plans to modify and update INCODE as additional evidence becomes available regarding potential causes of stillbirth.

Summary of key experiences with perinatal classification systems to consider for implementation of a successful global system

- No current systems meet the important characteristics of a global classification system as identified by expert users. However, based on work to date, it seems possible for such a system to be developed.
- Assigning a proximate reason for the death is challenging in many cases. Consideration should be given to multiple-cause coding and inclusion of degree of certainty for each judgement. Associated conditions should be clearly distinguished from causes
- Deaths that are unexplained must be differentiated from those unknown due to insufficient information (which may flag substandard investigation)
- The proportion of “unexplained” deaths must be reduced, without assigning a cause of death assigned that is not truly a cause
- Optimal evaluation is needed to ensure accurate cause-of-death data. In low resource settings, verbal autopsy may be the only source of information for classification and further research is needed on the utility of verbal autopsy for investigating stillbirths.
- Systems need to use clinically meaningful categories in order to maximise clinician acceptance and optimise implementation and therefore utility
- Training and support are needed to ensure effective, sustainable implementation.
- Placental pathology is important, but many placental pathologies are observed in livebirths. Further research is needed to assess which abnormalities are truly associated with stillbirth.

- Further research is needed on the relative merits of a hierarchical approach to classification
- "Closing the audit loop" to alter the behaviour of clinicians and managers to achieve the necessary practice change remains challenging and further research is needed

The first global classification system for perinatal deaths - ICD-PM

The WHO ICD-PM was released mid-2016 with guides for use following consultation and pilot testing using two datasets in South Africa and in the UK[30, 62-66]. It is modelled on the WHO ICD-Maternal Mortality (ICD-MM)[67] and uses the 10th revision of the ICD (ICD-10) and its rules. ICD-PM aims to enable user-friendly, consistent capture of causes of perinatal deaths to identify strategies to improve the health of both the mother and baby. ICD-PM has three distinct features: 1) it identifies the timing of death (antepartum, intrapartum, neonatal); 2) it identifies the cause of a perinatal death using ICD-10 categories that are grouped to enhance ease of use; and 3) the main maternal condition contributing to the death is also identified (including capture of absence of any conditions). All of the ICD-10 codes that can be assigned to the perinatal cause of death on a death certificate are represented in these groupings (see Table 1).

This system was applied in a pilot study to datasets from PIPP South Africa and the UK, even though the retrospective nature of the pilot may have resulted in diminished performance, the findings highlighted areas for improvements to prevent perinatal deaths[65]. In South Africa, programs addressing management of hypertension, improving intrapartum care, and the prevention of preterm birth were needed, and in the UK those addressing prematurity and the maternal and obstetric complications of the placenta, cord and membranes were highlighted[65]. In the South African dataset (using the definition of 1000g or 28 weeks' gestation), 53% of antepartum deaths were classified as "antepartum hypoxic events", which in itself would seem unhelpful for targeting future prevention. However, associated maternal conditions often provided an explanation for the death; mainly 'maternal hypertensive disorders' and 'complications of placenta cord and membranes' (which includes 'placental separation and haemorrhage' and a subcategory of 'abruptio placentae'). The second most common cause of antepartum fetal death was unspecified cause (42%); the majority (85%) without an identified maternal condition. Using the UK dataset (including deaths at 24 weeks' gestation or more), ICD-PM resulted in 48% of antepartum fetal deaths classified as unexplained, the majority with no maternal condition identified. Intrapartum deaths were mostly classified as "hypoxia related"; the maternal associated conditions shed light on the causal pathway with many being hypertension disorder and disorders of placental and membranes[65]. ICD-PM seemed to perform better for neonatal deaths with the majority due to consequences of low birth weight and prematurity; the majority with no associated maternal condition.

It is difficult to evaluate ICD-PM against the Delphi criteria for a good global system (according to users) as the system has not yet been implemented. ICD-PM currently satisfies 5 of 17 Delphi panel characteristics using the same methodology as Leisher and colleagues[9]. The strengths of ICD-PM against the expert user criteria include that it incorporates both stillbirths and neonatal deaths; it distinguishes between antepartum and intrapartum conditions; that associated factors are recorded and clearly distinguished from causes of death; that it has clear guidelines for use and definitions for all terms used; and that it has rules to ensure valid assignment of cause of death categories. The next revision of ICD provides an opportunity for improvements to ICD-PM which will be best informed with wide scale use and evaluation.

Operationalising a classification system

The WHO perinatal mortality audit guidelines "Making Every Baby Count Audit and review of stillbirths and neonatal deaths"[68] present the classification of perinatal deaths (using ICD-PM) in the context of high quality audit highlighting the need for a systematic approach to the establishment and maintenance of the audit. Findings from the international survey undertaken for the Lancet Ending Preventable Stillbirths series[12] suggests there is limited uptake of audit and classification of stillbirths across HICs. Less than 40% of care providers surveyed from HICs reported regular perinatal audit meetings were held at their facility and meetings rarely involved formal audit methodology[12]. Further analyses showed that less than half reported that a classification for cause of death is assigned for each case (Table 2). The majority (70%) were unsure which classification system was used to assign causes of death, and around 13% reported that no classification system was used, underscoring the importance of active implementation, even in high-resource settings.

Implementation

With ICD-PM based on death certificate data, successful implementation relies on improvements in certificate completion, which is notoriously inaccurate[69]. The WHO guidelines[68] which incorporates instructions for ICD-PM using ICD rules are a valuable tool. Specific training and support is essential to ensure success and WHO are developing a number of mechanisms to address this requirement. Experience with a relevant training program in Australia and some international settings indicates the value[58]. Replacing cumbersome paper-based systems with effective electronic systems can reduce work and improve access to outputs. Electronic health registries (eRegistries) enable centralised data collection throughout the continuum of care and across different services and providers[70]. Data collected may include vital events, coverage of essential interventions and associated maternal and perinatal morbidity[71], all critical to the accurate classification of causes of perinatal deaths and disaggregated analyses. eRegistries which facilitate tracking of clinical performance and feedback to providers and the general community, increase transparency and accountability needed for effective implementation of classification systems[70]. Finally, as maternal deaths are notifiable by national policy in an increasing number of high burden countries[72], maternal and perinatal mortality audits could be combined using a similar process to enhance efficiency.

Engagement of parents in perinatal audit

Audit and classification is critical to the counselling of parents following perinatal death. The dominant question many parents agonize over following the death their baby is *Why did this happen?*[12] A follow-up visit should be arranged as soon as possible after the perinatal mortality committee review to discuss the findings of diagnostic investigations. If the cause of death has changed as a result of the review a revised death certificate should be issued to the parents?[73] Parents want openness and honesty, and they want to know that preventive measures are being taken to reduce the numbers of parents that suffer the same tragedy in the future. Recent consultation with bereaved parents in the U.K., showed that they were largely unaware that a review of their child's death took place, and found it distressing that they were not involved or kept informed (project completed by DS and CS in 2015). Parents were unanimously in favour of an optional opportunity to contribute information, and would welcome a flexible system that could provide them with feedback, outcomes and lessons learned following the review.

Conclusions

Accurate classification of causes of perinatal death is an essential component of good clinical practice and should form part of a systematic approach to perinatal mortality audit wherever births occur, as set out by WHO[68]. The WHO ICD-PM is the first universal classification system and with widespread implementation has the potential to address the global burden of perinatal deaths. Successful implementation requires adequate resources, including staffing and effective data collection systems. This is of particular importance for LMIC settings. However, even in well-resourced settings, audit and classification is often undervalued and poorly implemented. High-level support is required to ensure quality national programs[12]. As no single classification system currently meets the needs of end users, identifying ways to ensure maximum engagement in ICD-PM is essential to ensure successful uptake. While awaiting future ICD-PM developments, use alongside other popular systems (e.g. more detailed systems in HIC) may prove helpful. Future research should focus on methods to evaluate system performance and different approaches to implementation, including an agreed list of core outcomes. Research to better understand and define the contribution of placental pathology to perinatal deaths is needed and international collaboration in this area is underway[74]. Another key area for future research is how best to engage parents in the audit process.

¥ The International Stillbirth Alliance Collaborative for Improving Classification of Perinatal Deaths

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VF and RMS developed the framework for the paper. VF led the manuscript writing integrating contributions received from authors. AMW carried out analyses of survey data. All authors provided feedback on the manuscript and reviewed and approved the final version of the before submission for publication.

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Conflict of interest statement

VF is the lead investigator for a National Health and Medical Research Council of Australia (NHMRC) Centre of Research Excellence in Stillbirth, and chair of the Intentional Stillbirth

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JJH is a member of the development team for the TULIP system

FF is lead developer for the CODAC system.

KP is a member of the development team for the Stockholm system

EMM is a member of the Global Network research stillbirth classification study[49]

ESD is the lead for the perinatal surveillance arm of MBRRACE-UK for the UK.

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Tables and Figures

Figure 1. Information sources for classification of stillbirths, by country setting

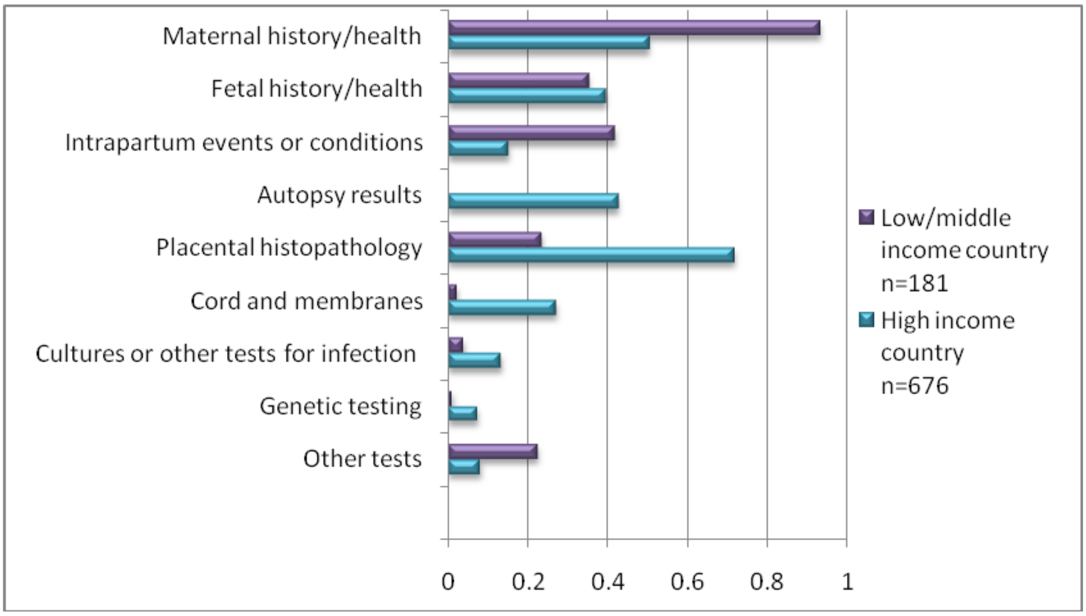

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Table 1. The ICD-PM system: perinatal causes of death, separated by timing of death, and maternal condition at the time of perinatal death

Main perinatal cause of death ICD-PM groups					
ANTEPARTUM DEATH		INTRAPARTUM DEATH		NEONATAL DEATH	
A1	Congenital malformations, deformations and chromosomal abnormalities	I1	Congenital malformations, deformations and chromosomal abnormalities	N1	Congenital malformations, deformations and chromosomal abnormalities
A2	Infection	I2	Birth trauma	N2	Disorders related fetal growth
A3	Antepartum hypoxia	I3	Acute intrapartum event	N3	Birth trauma
A4	Other specified antepartum disorder	I4	Infection	N4	Complications of intrapartum events
A5	Disorders related fetal growth	I5	Other specified intrapartum disorder	N5	Convulsions and disorders of cerebral status
A6	Antepartum death of unspecified cause	I6	Disorders related to fetal growth	N6	Infection
		I7	Intrapartum death of unspecified cause	N7	Respiratory and cardiovascular disorders
				N8	Other neonatal conditions
				N9	Low birth weight and prematurity
				N10	Miscellaneous
				N11	Neonatal death of unspecified cause
		MATERNAL CONDITION			
		M1	Complications of placenta, cord and membranes		
		M2	Maternal complications of pregnancy		
		M3	Other complications of labour and delivery		
		M4	Maternal medical and surgical conditions		
		M5	No maternal condition		

Table 2. International survey data on audit and classification of stillbirths across HICs

		N=1,884
		weighted %
Are regular perinatal audit meetings held at your facility?		
	Yes	38.4
	No	37.1
	Unsure	23.2
How often are these meetings held?[α]		
	Weekly	4.5
	Fortnightly or bimonthly	4.8
	Monthly	33.8
	Quarterly	26.1
	Yearly	5.6
	When a stillbirth occurs	3.7
	Unsure	18.2
How often do you attend these meetings?[α]		
	Never	24.1
	Rarely	6.8
	Sometimes	19.5
	Often	17.3
	Always	31.1
Are all cases of stillbirths reviewed?[α]		
	Yes	64.3
	No	13.8
	Unsure	21.7
Who attends the perinatal audit meetings? [α β]		
	Obstetricians	89.6
	Midwives	64.1
	Obstetric nurses	48
	Paediatricians	43.3
	Pathologists	32
	Gynaecologists	24.7
	Social workers	21
	Other	11
Is the hospital perinatal audit part of a national approach?[α]		
	Yes	19.3
	No	28.7
	Unsure	52
Do the meetings involve case discussions only, or formal audit methodology?[α]		
	Case discussions only	62.1
	Formal audit methodology	11.6
	Unsure	25.8
Is a classification for cause of death assigned for each case reviewed?[α]		
	Never	10.5

		N=1,884
		weighted %
	Rarely	1.4
	Sometimes	12.7
	Often	19.8
	Always	24.4
	Unsure	30.9
Which classification system is used to assign a cause of death?[α,β]		
	None	13.2
	Aberdeen	<1
	Codac	4
	INCODE	2.1
	PSANZ-PDC	<1
	ReCoDe	1.1
	TULIP	4.5
	Wigglesworth	1.5
	Other	4.1
	Unsure	69.6
Are clinical care standards relating to stillbirth discussed?[α]		
	Never	2.7
	Rarely	1.1
	Sometimes	26.6
	Often	28
	Always	17.3
	Unsure	24
Is the outcome of review of clinical care used to improve practice?[α]		
	Never	2.2
	Rarely	1.4
	Sometimes	25.2
	Often	35.3
	Always	22.4
	Unsure	13.4

HICs: High-income countries; Codac: Causes of death and associated conditions; INCODE: Initial causes of fetal death; PSANZ-PDC: Perinatal Society of Australia and New Zealand Perinatal Death Classification; ReCoDe: Relevant condition at death

Data were weighted to account for uneven distribution of responses across countries

Where percentages <100, remainder of participants provided no response

[α] Denominator based on respondents who answered “Yes” to “Are regular perinatal audit meetings held at your facility?”

[β] Multiple responses permitted

Appendices

Appendix 1 Evaluation of best performing systems against expert criteria

		Codac (9/17)	Tulip (7/17)	PSANZ-PDC (6/17)	CHERG (6/17)	Cole 1986 (6/17)	Kotecha 2014 (6/17)	Ujwala 2012 (6/17)
1	A global system must use rules to ensure valid assignment of cause of death categories.	Yes	Yes	Yes	Yes	Yes	Yes	No
2	A global system must be able to work with all levels of data (from both low-income and high-income countries), including minimal levels.	No	No	No	Yes	No	No	No
3	A global system must ensure cause of death categories are relevant in all settings.	No	No	Yes	Yes	Yes	No	No
4	A global system must require associated factors to be recorded and clearly distinguished from causes of death.	Yes	Yes	Yes	No	No	No	No
5	A global system must distinguish between antepartum and intrapartum conditions.	Yes	No	No	No	No	No	Yes
6	A global system should record the level of data available to assign the cause of death (e.g. verbal autopsy only, placental histology, autopsy, etc.).	Yes	No	No	No	No	No	No
7	A global system must have multiple levels of causes of death, with a small number of main categories.	Yes	Yes	Yes	No	Yes	No	Yes
8	A global system must include a sufficiently comprehensive list of categories to result in a low proportion of deaths classified as "other".	Yes	Yes	No	Yes	No	Yes	Yes
9	A global system must be easy to use, and produce data that are easily understood and valued by users.	No	No	No	No	No	No	No

		Codac (9/17)	Tulip (7/17)	PSANZ-PDC (6/17)	CHERG (6/17)	Cole 1986 (6/17)	Kotecha 2014 (6/17)	Ujwala 2012 (6/17)
10	A global system must have clear guidelines for use and definitions for all terms used.	No	No	No	No	Yes	Yes	No
11	A global system must produce data that can be used to inform strategies to prevent perinatal deaths.	No	No	No	No	No	No	No
12	A global system must require neonatal deaths to be clearly distinguished from stillbirths.	No	No	No	No	No	No	No
13	A global system must have high inter- and intra-rater reliability.	No	Yes	Yes	No	No	No	Yes
14	A global system must be available in different formats including inexpensive ehealth and mhealth options, and in multiple languages.	No	No	No	No	No	No	No
15	A global system must allow easy access to the data by the end-users.	Yes	No	No	Yes	No	Yes	No
16	A global system must incorporate both stillbirths and neonatal deaths	Yes	Yes	Yes	No	Yes	Yes	Yes
17	A global system must require the single most important factor leading to the death to be recorded.	Yes	Yes	No	Yes	Yes	Yes	Yes

Data complied from that reported in: Leisher SH, Teoh Z, Reinebrant H, Allanson E, Blencowe H, Erwich JJ, et al. Classification systems for causes of stillbirth and neonatal death, 2009-2014: an assessment of alignment with characteristics for an effective global system. BMC Pregnancy Childbirth. 2016;16:269.