Making stillbirths visible: A systematic review of globally reported causes of stillbirth

Short title: Global reporting of causes of stillbirth

Authors

Hanna E Reinebrant[a,b], Susannah Hopkins Leisher[a,b], Michael Coory[c,d], Sarah Henry[a,b], Aleena M Wojcieszek[a,b], Glenn Gardener[a,b], Rohan Lourie[a,e], David Ellwood[f,g], Zheyi Teoh[a,h], Emma Allanson[i,j], Hannah Blencowe[k], Elizabeth S Draper[l], Jan Jaap Erwich[b,m], J Frederik Frøen[n,o], Jason Gardosi[p], Katherine Gold[b,q], Sanne Gordijn[b,m], Adrienne Gordon[r], Alexander EP Heazell[s,t], Teck Yee Khong[u], Fleurisca Korteweg[v], Joy E Lawn[k], Elizabeth M McClure[b,w], Jeremy Oats[x,y], Robert Pattinson[z], Karin Pettersson[1], Dimitrios Siassakos[b,2], Robert M Silver[3], Gordon Smith[4], Özge Tunçalp[i], Vicki Flenady[a,b]

Affiliations

[a] Centre of Research Excellence in Stillbirth, Mater Research Institute, The University of Queensland (MRI-UQ), Brisbane, Australia

[b] International Stillbirth Alliance, Bristol, UK

[c] Murdoch Childrens Research Institute, Melbourne, Victoria, Australia

[d] Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia

[e] Translational Research Institute, Brisbane, Queensland, Australia

[f] Griffith University School of Medicine, Queensland, Australia

[g] Gold Coast University Hospital, Gold Coast, Queensland, Australia

[h] University of Louisville, Department of Medicine-Pediatrics, Louisville, KY, USA

[i] Department of Reproductive Health and Research including UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), World Health Organization, Geneva, Switzerland

[j] School of Women's and Infants' Health, Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, Perth, Australia

[k] London School of Hygiene & Tropical Medicine, London, UK

[l] MBRRACE-UK, Department of Health Sciences, University of Leicester Centre for Medicine, Leicester, UK

[m] University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[n] Norwegian Institute of Public Health, Oslo, Norway

[o] Centre for Intervention Science in Maternal and Child Health (CISMAC), University of Bergen, Bergen, Norway

[p] Perinatal Institute, Birmingham, UK

[q] Department of Family Medicine and Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA

[r] University of Sydney, Sydney, Australia

[s] Division of Developmental Biomedicine, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK

[t] St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

[u] SA Pathology, Women's and Children's Hospital, North Adelaide, Australia

[v] Department of Obstetrics and Gynecology, Martini Hospital, Groningen, The Netherlands

[w] Department of Social, Statistical and Environmental Health Sciences, Research Triangle Institute, Research Triangle Park, NC, USA

[x] Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia

[y] Consultative Council on Obstetrics and Paediatric Mortality and Morbidity (CCOPMM), Victoria, Australia

[z] Department of Obstetrics and Gynaecology, University of Pretoria, Pretoria, South Africa

[1] Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

[2] University of Bristol, School of Social and Community Medicine, Obstetrics and Gynaecology, Southmead Hospital, Bristol, UK

[3] University of Utah School of Medicine, Salt Lake City, UT, USA

[4] Department of Obstetrics and Gynaecology, University of Cambridge, NIHR Cambridge Comprehensive Biomedical Research Centre, Cambridge, UK

Correspondence

Hanna Reinebrant, Mater Research Institute - The University of Queensland (MRI-UQ), Level 3, Aubigny Place, South Brisbane, Qld, 4101, Australia. Email: hanna.reinebrant@mater.uq.edu.au, Phone: +61731632119

Abstract

Background

Stillbirth is a global health problem. The World Health Organization (WHO) application of the International Classification of Diseases for perinatal mortality (ICD-PM) aims to improve data on stillbirth to enable prevention.

Objectives

To identify globally reported causes of stillbirth, classification systems, and alignment with the ICD-PM.

Search strategy

We searched CINAHL, EMBASE, Medline, Global Health, and Pubmed from 2009 to 2016.

Selection criteria

Reports of stillbirth causes in unselective cohorts.

Data collection and analysis

Pooled estimates of causes were derived for country representative reports. Systems and causes were assessed for alignment with the ICD-PM. Data are presented by income setting (low, middle, and high income countries; LIC, MIC, HIC).

Main results

Eighty-five reports from 50 countries (489 089 stillbirths) were included. The most frequent categories were Unexplained, Antepartum haemorrhage, and Other (all settings); Infection and Hypoxic peripartum (LIC), and Placental (MIC, HIC). Overall report quality was low. Only one

classification system fully aligned with ICD-PM. All stillbirth causes mapped to ICD-PM. In a subset from HIC, mapping obscured major causes.

Conclusions

There is a paucity of quality information on causes of stillbirth globally. Improving investigation of stillbirths and standardisation of audit and classification is urgently needed and should be achievable in all well-resourced settings. Implementation of the WHO Perinatal Mortality Audit and Review guide is needed, particularly across high burden settings.

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Tweetable abstract

Urgent need to improve data on causes of stillbirths across all settings to meet global targets.

Plain Language Summary

Background and methods

Nearly three million babies are stillborn every year. These deaths have deep and long-lasting effects on parents, healthcare providers, and the society. One of the major challenges to preventing stillbirths is the lack of information about why they happen. In this study, we collected reports on the causes of stillbirth from high-, middle-, and low-income countries to: (1) Understand the causes of stillbirth, and (2) Understand how to improve reporting of stillbirths.

Findings

We found 85 reports from 50 different countries. The information available from the reports was inconsistent and often of poor quality, so it was hard to get a clear picture about what are the causes of stillbirth across the world. Many different definitions of stillbirth were used. There was also wide variation in what investigations of the mother and baby were undertaken to identify the cause of stillbirth. Stillbirths in all income settings (low-, middle-, and high-income countries) were most frequently reported as *Unexplained*, *Other*, and *Haemorrhage (bleeding)*. *Unexplained* and *Other* are not helpful in understanding why a baby was stillborn. In low-income countries, stillbirths were often attributed to *Infection* and *Complications during labour and birth*. In middle- and high-income countries, stillbirths were often reported as *Placental complications*.

Limitations

We may have missed some reports as searches were carried out in English only. The available reports were of poor quality.

Implications

Many countries, particularly those where the majority of stillbirths occur, do not report any information about these deaths. Where there are reports, the quality is often poor. It is important to improve the investigation and reporting of stillbirth using a standardised system so that policy makers and healthcare workers can develop effective stillbirth prevention programs. All stillbirths should be investigated and reported in line with the World Health Organization standards.

Introduction

The global stillbirth rate (≥28 completed weeks' gestation) is estimated to be 18.4 per 1000 births[1] or around 2.6 million stillbirths each year[1]. The World Health Organization's (WHO's) Every Newborn Action Plan aims to reduce the stillbirth rate to 12 or fewer per 1000 births by 2030 in every country, and for countries already meeting this target to reduce equity gaps[2]. However, with an estimated annual reduction rate of 2.0% between 2000 and 2015[1], half that for neonatal deaths, progress has been slow. Identifying interventions to achieve such a target would be facilitated by cross-country and inter-country comparisons of the causes of stillbirth. Moreover, while national neonatal causes of death are regularly published through the United Nations[1,3], there is currently no systematic global reporting of causes of stillbirth. The WHO recommends use of the International Statistical Classification of Diseases and Health Related Problems (ICD) for classification of perinatal deaths for international reporting[4]. However, limitations in ICD for classifying stillbirths[5] has resulted in numerous disparate systems currently in use[6], thus limiting global comparisons. In 2016, WHO released ICD Perinatal Mortality (ICD-PM) as part of the WHO Perinatal Mortality Audit and Review guide[7]. The ICD-PM is an application of ICD and holds promise as an important step in improving global and local reporting of causes of stillbirths and neonatal deaths[8]. The ICD-PM aims to collect, at a minimum, timing of death and clinically defined causes and associated conditions.

Objectives

Following on the introduction of the ICD-PM, we aimed to identify globally reported causes of stillbirth in order to support progress toward the WHO Every Newborn Action Plan stillbirth rate target. The specific objectives were to:

1. Describe the current status of global reporting of stillbirth causes, including reported causes and classification systems used;
2. Pool results from country representative reports to identify commonly reported causes of stillbirth, stratified by income setting (high-, middle-, and low-income); and

3. Assess alignment of systems used and reported causes of stillbirths with the ICD-PM for country representative reports.

Methods

This systematic review was conducted and reported according to the PRISMA checklist[9]. The protocol has not been published. Two authors independently undertook screening of reports, selection, data extraction and quality assessment.

Eligibility criteria

All published and unpublished cohort and cross-sectional reports from 1 January 2009 to 31 December 2016 which presented causes of stillbirth were eligible. Reports were excluded if they: included non-consecutive or selected subgroups, e.g. preterm; aimed only to identify risk factors or did not provide data on causes in an extractable format (for complete study selection see Figure S1).

Information sources

We searched PubMed, Global Health, Cinahl, Medline and Embase without language restrictions. We identified national reports through web-based systematic searches (Appendix S1) and cross-referenced included reports.

Study selection

Titles and abstracts of identified reports were screened for eligibility; full text papers were retrieved if potentially eligible or unsure. All reports presenting causes of stillbirth were included to address Objective 1. To address Objectives 2 and 3, the most recent national report for each country was selected. If a national report was unavailable, a report was selected on criteria (in descending order): 1) population-based report with the largest number of stillbirths, 2) multi-centre health facility report covering the largest population.

Data extraction

A purpose built data extraction form was used. For details on data items and definitions used, see Additional Information S2.

Grouping reported stillbirth causes

The development of categories and mapping of reported causes of stillbirth to categories were undertaken by a panel including Maternal Fetal Medicine Specialists (GG, BS, DE), pathologist (RL) and epidemiologist (VF), with guidance from The Amsterdam Classification Workshop[10] members. Categories were created by "clustering" reported causes into 15 clinically meaningful groups for stillbirth prevention ("global categories") (Table S1). With the addition of *Placental conditions*, these categories generally coincided with previously suggested major causal groupings by Lawn et al[11]. We did not attempt to differentiate causes from associated conditions (Table S1).

Quality assessment

Quality assessment of country representative reports included in the pooled analysis of reported causes was performed using an adapted version of the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data[12] (Appendix S3). An overall quality rating was derived for each report (low, medium, or high quality). For subgroup analyses of "good" quality reports, we combined data from reports assessed as high and medium quality.

Data presentation and analysis

Data were presented by income setting using World Bank groupings[13] of low and lower-middle (LIC; Gross National Income (GNI) ≤$3,955), upper-middle (MIC; GNI $3,956- $12,235) and high (HIC; GNI ≥$12,236). Categories of stillbirth causes were presented as proportions of the total number of stillbirths classified. Results from country representative reports were statistically pooled to identify commonly reported causes stratified by country groupings. Analyses were done in R using the meta package[14] with 95% prediction intervals (PI)[15-17] (Appendix S4). Subgroup analyses by report quality and type of system (ICD versus clinical classification systems) were planned *a priori*. See Appendix S2 for definition of clinical classification systems[6] and criteria for alignment of classification systems with ICD-PM.

Each reported cause was mapped to the relevant ICD-PM major category. The ICD-PM includes five major maternal condition categories (M1-5) and 13 fetal categories, six with antepartum timing (A1-

6) and seven with intrapartum timing (I1-7)[4]. For the Unknown (U) timing category we included the categories: U1: *Congenital malformations, deformations and chromosomal abnormalities*; U2: *Infection*; U3: *Other specified disorder*; U4: *Disorders related to fetal growth*; U5: *Death of unspecified cause*. We added one category, *Other*, to all timings to accommodate the causes without ICD-PM coding.

The proportions of stillbirths that could be mapped to a fetal cause and/or a maternal condition in ICD-PM were calculated. Mapping of data from good quality HIC reports to ICD-PM was compared descriptively with the 15 global categories.

Results

Of 7415 abstracts screened for eligibility, 909 full-text papers were reviewed for inclusion and 824 records were excluded: did not discuss stillbirth (396), no extractable data (217), sub-populations only (145), risk factors only (12) (for complete study selection see Figure S1). Eighty-five reports (LIC 28, MIC 20, HIC 37) with a total of 489,089 stillbirths were included in the review (LIC 13,197, MIC 431,216, HIC 44,676). Thirty-three country representative reports classifying 454,533 stillbirths were included in the pooled analysis of causes and mapping to ICD-PM.

Global stillbirth reporting

Description of included reports

The 85 included reports originated from 50 countries. Reports were published in English (66) and non-English (19; Table S2). Eleven reports excluded terminations of pregnancy. Half of the reports (including 2.4% of all stillbirths) were from hospital settings (LIC: 19 reports/7419 stillbirths; MIC: 8 reports/1134 stillbirths; HIC: 16 reports/3240 stillbirths) (Table 1, for full details see Table S2).

Definitions of stillbirth

Stillbirth was defined in 71 reports (84%) using 34 discrete definitions (Figure S2). The majority of HIC reports (78%) used a lower gestational age limit of 20-24 weeks while the majority of LIC reports (68%) used 28 weeks (Table 1).

Table 1. Characteristics of included papers. By income setting (85 reports; 489 089 stillbirths)

	All reports				Country representative reports			
	HIC ***n*** **= 37**	**MIC** ***n*** **= 20**	**LIC** ***n*** **= 28**	**Total** ***n*** **= 85**	**HIC** ***n*** **= 15**	**MIC** ***n*** **= 11**	**LIC** ***n*** **= 7**	**Total** ***n*** **= 33**
	n **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**	***n*** **(%)**
Countries included	20	14	15	49	15	11	7	33
Stillbirths classified	44 676	431 203	13 197	489 089	19 238	429 666	5629	454 533
Stillbirth definition								
20–24 weeks	29 (78)	10 (50)	5 (18)	44 (52)	13 (87)	4 (36)	0	17 (52)
28 weeks	2 (5)	6 (30)	19 (68)	27 (32)	2 (13)	3 (27)	4 (57)	9 (27)
Unknown	6 (16)	4 (20)	4 (14)	14 (16)	0	3 (27)	2 (29)	5 (15)
Terminations								
Excluded	9 (24)	2 (10)	0	11 (13)	2 (13)	0	0	2 (6)
Unknown	19 (51)	14 (70)	25 (89)	58 (68)	7 (47)	8 (73)	6 (86)	21 (64)
Multiple pregnancies								
Excluded	5 (14)	1 (5)	3 (11)	9 (11)	1 (7)	0	1 (14)	2 (6)
Unknown	11 (30)	12 (60)	8 (29)	31 (36)	4 (27)	8 (73)	1 (14)	13 (39)
Setting								
Population based	21 (57)	12 (60)	8 (29)	41 (48)	15 (100)	11 (100)	6 (86)	32 (97)
Hospital based	16 (43)	8 (40)	19 (68)	43 (51)	0	0	1 (14)	1 (3)
Unknown	0	0	1 (4)	1 (1)	0	0	0	0
Language								
English	33 (89)	7 (35)	26 (93)	66 (78)	11 (73)	2 (18)	6 (86)	19 (58)
Non-English	4 (11)	13 (65)	2 (7)	19 (22)	4 (27)	9 (82)	1 (14)	14 (42)
Classification systems								
ICD	14 (38)	7 (35)	3 (11)	24 (28)	9 (60)	7 (64)	1 (14)	17 (52)
Clinical classification system	20 (54)	6 (30)	15 (54)	41 (48)	6 (40)	2 (18)	3 (43)	11 (33)
No system	3 (8)	7 (35)	10 (36)	20 (24)	0	2 (18)	3 (43)	5 (15)

- HIC, high-income countries; ICD, International Classification of Diseases; LIC, low-income countries; MIC, middle-income countries; Terminations, termination of pregnancy.

Data available to classifiers

Systematic prospective perinatal mortality audits were used in 21 reports (LIC 2, MIC 4, HIC 15), of which 12 were hospital audits; seven used comprehensive investigation protocols (all from HIC) (Table S2). In 40 reports, retrospective audit data were used; 18 of these (LIC 2, MIC 6, HIC 10) sourced causes from Civil Registration and Vital Statistics (CRVS). Sixteen reports (LIC 13, MIC 3) were prospective studies; eight of these, all from LIC, used verbal autopsy. Reported autopsy rates in 20 reports [MIC 3 (14%), HIC 17 (47%)] ranged from 2.7% to 100%. In over half of the reports (55%) it was unclear whether autopsy had been performed. Placental pathology examination rates

were included in 15 reports (18%) (none in LIC) with rates ranging from 22% to 100%. For full details on data available see Table S2.

Classification systems

Twenty-one clinical classification systems[18-38] were used in 41 of the 85 reports (LIC 15 reports/30% of stillbirths, MIC 6 reports/5% of stillbirths, HIC 20 reports/27% of stillbirths). The ICD was used more frequently in HIC (14 reports/72% of stillbirths) and MIC (7 reports/94% of stillbirths) than LIC (3 reports/2% of stillbirths) (Table 1). The remaining 20 reports listed causes of death without reference to any classification system. Areas of origin for the 21 clinical systems is shown in Table S3. Three-quarters of the systems allow a single primary cause of death, and half the systems allow associated factors to be recorded (Table S4). Five systems provide comprehensive definitions of causes[20,27,30-32] and 13 systems provide rules for assigning cause of death (See Table S4 for full details on clinical classification systems).

Globally reported categories of stillbirth

The 85 included reports presented causes of stillbirth using 860 unique terms. These were grouped into 15 global categories and 46 minor categories, of which eight major categories were common to over half (53%) of the reports (Table S5).

Congenital anomalies was the most frequently reported category, included in 93% of all reports. The proportion of stillbirths assigned to this category ranged from 1.4% in Nigeria[39] to 64.4% in China[40] (Figure 1, Table S5). The second category was *Unexplained*, included in 82% of all reports, ranging from 0.3% in Turkey[25] to 82.0% in Japan[41]. *Maternal conditions* were included in 64% of all reports, with frequency ranging from 0.6% in Ireland[42] to 36.5% in Italy[28] (Figure 1, Table S5).

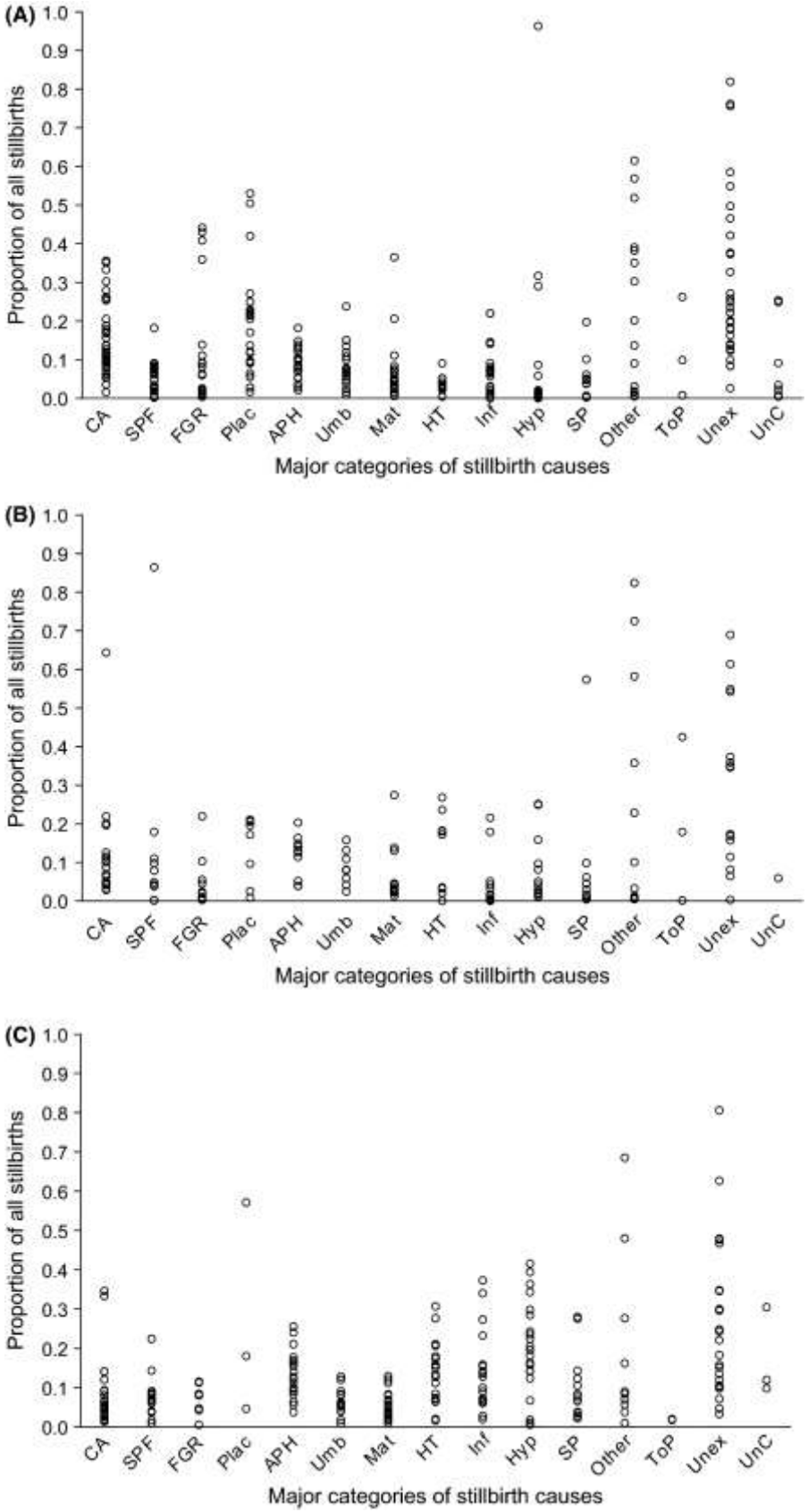


Figure 1. Proportion of stillbirths in each category for all studies. By income setting (85 reports; 489 089 stillbirths). (A) Reports from high-income countries (HIC): 37 reports with 44 676 stillbirths. (B) Reports from middle-income countries (MIC), 20 reports with 431 216 stillbirths. (C) Reports from low-income countries (LIC): 28 reports with 13 197 stillbirths. APH, antepartum haemorrhage; CA, congenital anomalies; FGR, fetal growth restriction; HT, hypertension; Hyp, hypoxic peripartum death; Inf, infection; Mat, maternal conditions; Other, other unspecified condition; Plac, placental conditions; SP, spontaneous preterm; SPF, specific fetal/placental condition; ToP, termination of pregnancy, unspecified; Umb, umbilical cord; UnC, unable to classify; Unex, unexplained.

The proportions of categories also differed across type of classification system. The most commonly reported categories for reports using the ICD included *Other unspecified condition* (68% of reports) and *Hypoxic peripartum death* (64%), whereas for clinical systems these included *Antepartum haemorrhage* (72%) and *Infection* (67%).

Country representative reports

Description of included reports

Thirty-three reports classifying 454,533 stillbirths were included in the pooled analysis: seven LIC (5,629 stillbirths), 11 MIC (429,666 stillbirths), and 15 HIC (19,238 stillbirths). Twenty-one reports included ≥95% of total stillbirths in the country during the reporting period, one report included 72%, three included 6-49% and eight included ≤5% (Figure S3). In two reports (6%), terminations of pregnancy were excluded, and in 21 (64%), no reference was made to terminations. The ICD was used mainly in HIC and MIC reports (60% and 64%, respectively, versus 14% of LIC reports; Table 1, Table S2).

Quality assessment identified 13 good quality reports (29% of all LIC reports, 36% of all MIC reports, 47% of all HIC reports); only one of these was high-quality[43]. The remaining reports were assessed as low-quality (Table S6, Figure S4).

Pooled estimates of commonly reported causes of stillbirths

The top five categories by frequency for each country grouping are shown in Figure 2. *Unexplained* was the top category across all settings, with pooled estimated ranging from 31.2% to 43.7% (Tables S7, S8). Two additional categories were amongst the top five across all settings: *Other unspecified conditions* (9.3% to 11.6%) and *Antepartum haemorrhage* (8.4% to 9.3%; Tables S7, S9, S10). In LIC, *Infection* (15.8%) and *Hypoxic peripartum death* (11.6%; Tables S7, S11, S12) were also amongst the top five. In both HIC and MIC settings *Placental conditions* (14.4% and 13.7%, respectively) ranked in the top five, with C*ongenital anomalies* as the remaining category in HIC (14.0%) and *Specific fetal/pregnancy pathology* in MIC (11.0%) (Tables S7, S13, S14, S15).

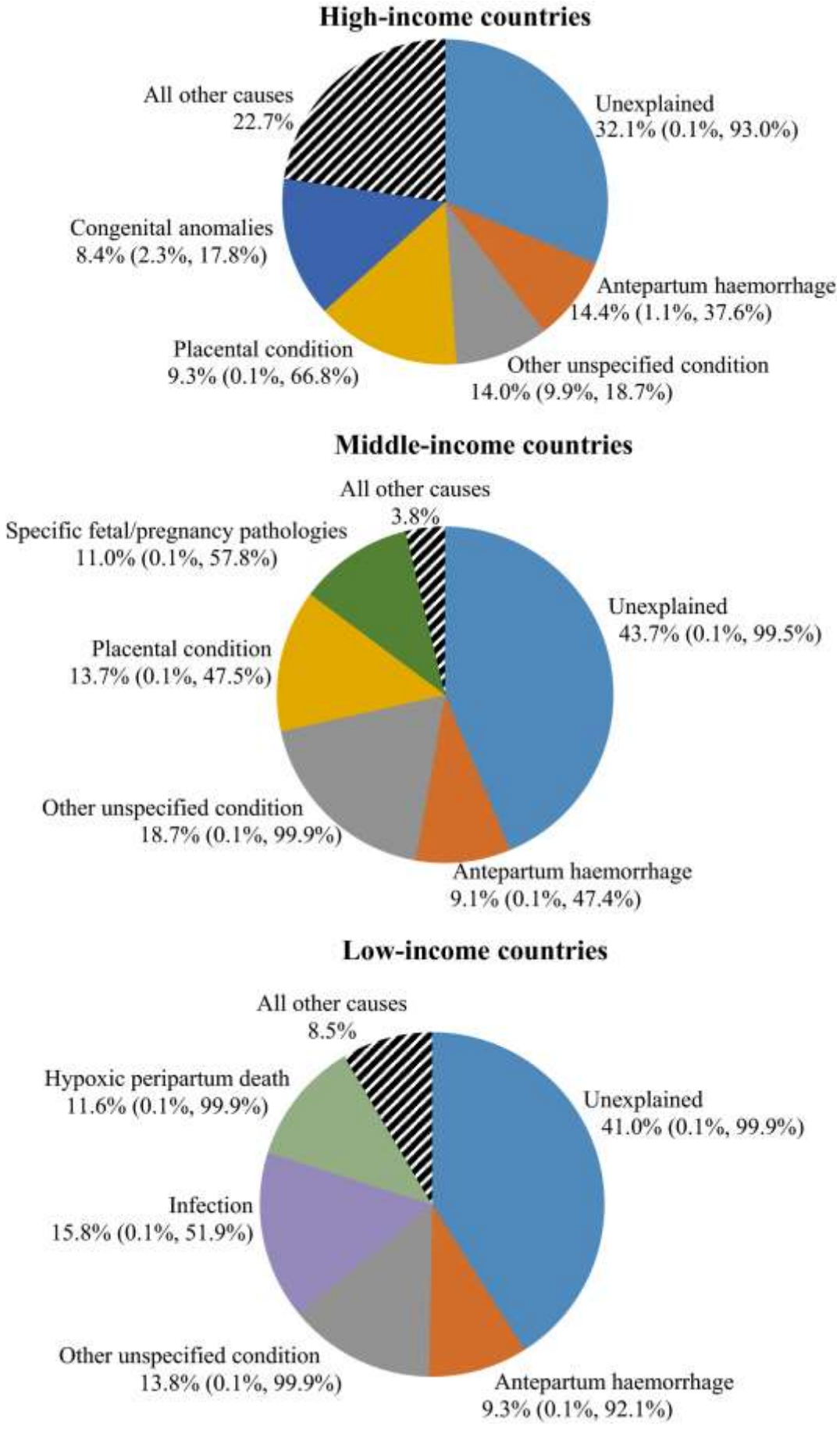


Figure 2. Top five pooled estimates of the global categories of stillbirth. Country-representative reports by income setting (33 reports, 454 533 stillbirths). Data presented as point estimate (95% prediction interval).

Details of pooled analyses of *Umbilical cord complications*, *Maternal conditions*, *Spontaneous preterm*, *Hypertension*, *Fetal growth restriction* and *Terminations* are presented in Tables S16-S21.

Sub-group analysis

Due to insufficient data subgroup analysis by report quality was only possible for HIC. The proportion of *Unexplained* (15.4% vs 31.6%) and *Other unspecified conditions* (1.6% vs 9.3%) was lower in good quality reports versus all reports (Tables S8, S9). Subgroup analyses by system type showed higher proportions of *Antepartum haemorrhage* using clinical systems (14.1%) than using ICD (4.4%) in MIC (Table S10). Use of clinical systems resulted in lower proportions of *Other unspecified conditions* (1.6%) and *Unexplained* (17.7%) than use of ICD (13.2% and 43.4%, respectively) in HIC (Tables S9, S8).

Alignment with the ICD-PM

Alignment of clinical classification systems with the ICD-PM

Of 21 classification systems used, only Codac[19] was fully aligned with the ICD-PM. Four systems met two of the three criteria used to assess alignment, and 14 systems scored 0.5-1.5 out of a maximum of 3 (Table S3, Figure S5).

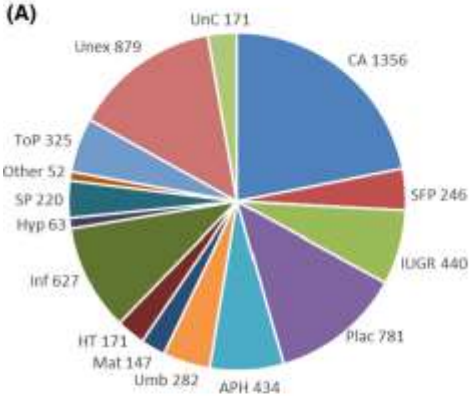
Mapping of reported causes to ICD-PM

Nearly all the 454,533 stillbirths reported in the 33 country representative reports were mapped to an ICD-PM fetal or maternal category, or both. Causes for 831 stillbirths (0.2%) mapped to ICD-PM neonatal rather than fetal codes (for example "neonatal aspiration syndrome"). 264,480 stillbirths (58%) were mapped to a fetal but not a maternal ICD-PM cause, and 140,319 (31%) to a maternal but not a fetal ICD-PM cause; 49,734 stillbirths (11%) were mapped to both (Tables S22, S23).

Of the 204,545 stillbirths in the global category *Unexplained*, 113,558 (56%) were mapped to the ICD-PM category *Unknown timing unspecified* (no maternal condition), 90,335 (44%) to *Antepartum hypoxia* (no maternal condition), 602 (0.3%) to *Antepartum unspecified* (no maternal condition), and 50 (0.02%) to maternal condition *Other complications of labour and delivery* (no fetal cause) (Tables S22, S23).

The global causes from best available data (good quality reports using clinical classification systems in HIC, five reports; 6,194 stillbirths) were mapped to ICD-PM. The global categories reflecting underlying placental causes of *Antepartum haemorrhage* and *Placental condition* (insufficiency) accounted for 20%, and *Intrauterine growth restriction* 7% of stillbirths (Figure 3). When mapped to the ICD-PM, these global categories are included within the major maternal category *Complications of placenta, cord and membrane*s and the fetal category *Disorders related to fetal growth*, accounting for 30% and 17% of stillbirths, respectively (Figure 3).

(A)



(B)

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 identified	Total
Antepartum						
A1: Congenital malformations	0	0	0	0	0	0
A2: Infection	0	0	0	0	0	0
A3: Antepartum hypoxia	0	0	0	0	0	0
A4: Other specified antepartum disorder	0	0	0	0	0	0
A5: Disorders related to fetal growth	0	0	0	0	0	0
A6: Antepartum death of unspecified cause	21	0	0	0	597	618
A7: Other	0	0	0	0	0	0
Total	21	0	0	0	597	618
Intrapartum						
I1: Congenital malformations	0	0	0	0	0	0
I2: Birth trauma	0	0	0	0	2	2
I3: Acute intrapartum event	0	0	5	0	56	61
I4: Infection	208	0	0	0	0	208
I5: Other specified intrapartum	0	0	0	0	0	0
I6: Disorders related to fetal growth	0	1	0	0	187	188
I7: Intrapartum death of unspecified cause	0	0	0	0	0	0
I8: Other	0	0	0	0	0	0
Total	208	1	5	0	245	459
Unknown timing						
U1: Congenital malformations	0	0	0	0	1344	1344
U2: Infection	0	0	0	248	128	376
U3: Other specified disorder	90	0	0	59	405	554
U4: Disorders related to fetal growth	435	0	0	17	440	892
U5: Death of unspecified cause	0	0	0	0	511	511
U6: Other	0	0	0	0	0	0
Total	525	0	0	324	2828	3677
No fetal cause	1091	59	0	290	0	1440
Total	**1845**	**60**	**5**	**614**	**3670**	**6194**

Figure 3. Mapping of causes from good quality reports using clinical classification systems from high income countries (5 reports; 6,194 stillbirths). (A) Grouping of causes of stillbirths into 15 global categories. (B) Stillbirths mapped to the ICD-PM matrix. APH, antepartum haemorrhage; CA, congenital anomalies; FGR, fetal growth restriction; HT, hypertension; Hyp, hypoxic peripartum death; Inf, infection; Mat, maternal conditions; Other, other unspecified condition; Plac, placental conditions; SPF, specific fetal/placental condition; SP, spontaneous preterm; ToP, termination of pregnancy, unspecified; Umb, umbilical cord; UnC, unable to classify; Unex, unexplained.

Discussion

Main findings

From 85 reports presenting causes of nearly half a million stillbirths from 50 countries and all income settings, we identified 15 major causal categories from nearly 900 causal terms; eight categories were common to the majority of reports. Despite this overarching commonality, we found wide variation

in frequency of stillbirth categories and in the systems used to classify them with generally poor quality data. Underlining one of the key challenges of achieving the Every Newborn Action Plan stillbirth target, are the high proportions of stillbirths without information to guide prevention (*Unexplained* and *Other unspecified conditions)* in all income settings.

Strengths and limitations

We sought to include the most detailed causes of stillbirth available to allow identification of common groupings, and ultimately to enable consistent reporting across settings. In line with WHO recommendations[4,44] and to maximize the utility of the data for prevention strategies, we excluded reports which assigned more than one cause of stillbirths and excluded all those reported as associated only. This may have resulted in a loss of information and limited our ability to assess the full value of the ICD-PM, which aim to record both a fetal and a maternal condition for every stillbirth. The need to assign multiple causes for some stillbirths has been highlighted. Further, the distinction between causes and associated conditions is often poorly defined[26] and in this review many reported "causes" are not recognised as causal conditions. Further, although we imposed no language restriction, we may have missed some reports due to English-language search terms.

Interpretation

Data quality

Data quality was generally poor with only a small number of reports based on high quality perinatal mortality audit. Further, many reports did not provide sufficient detail to adequately assess quality. Similar to others[1,5,45], we found global comparisons problematic due to differing definitions and systems. The inability to identify termination of pregnancies in reporting of stillbirth causes is problematic; many are terminated as a consequence of congenital anomalies[46], some of which may not have resulted in stillbirth.

Global causes of stillbirth

Results of the pooled analysis enabled comparisons of stillbirth causes across settings, providing additional evidence for key areas for prevention. The relatively high proportion of stillbirths attributed

to intrapartum hypoxia (*Hypoxic peripartum*) in LIC versus HIC and MIC is in line with recent evidence from low- and middle-income countries (LMIC)[47,48] and confirms the urgency of improving care during labour and birth, when half of all global stillbirths occur[1,3,47,49]. Further, similar to other reports[47,48] we identified infection as a top cause of stillbirths in LIC, confirming the importance of infection prevention and management[3,49,50]. Our findings clearly highlight the importance of placental conditions as a major contributor to stillbirths in all settings, consistent with other recent studies[47,51]. However, many placental conditions were ill-defined and the causal link unclear (for instance delayed villous maturation)[52,53]. Many conditions that lead to stillbirth are also linked to neonatal deaths and therefore both must be accommodated within a single system to ensure optimal pregnancy care and outcomes[54].

ICD-PM and progress towards global reporting

We confirmed findings of other studies, showing numerous disparate systems for classification of stillbirths in use globally[5,45,55], further highlighting the need for a globally effective classification system. A recent consensus described user-identified characteristics for such a system[56], however no existing systems meet these characteristics[57]. Further, robust evaluation of system performance is limited[6]. The ICD-PM is the first system intended for global use in classification of perinatal deaths[4,58-60], aiming to facilitate comparisons by improving perinatal mortality data, particularly in high burden settings. While evaluation of the performance of ICD-PM is currently limited, retrospective application to datasets in the UK and South Africa highlighted its values and provided insights to future improvements[59]. In our dataset, all causes of stillbirths reported globally could be accommodated within the ICD-PM. However, our mapping of causes from good quality reports in HIC using clinical classification systems highlights that classification system needs differ across settings. Meeting the needs of diverse settings is essential for global comparisons to identify important variation and inform programmatic change to reduce deaths.

The WHO Perinatal Mortality Audit and Review guide[7] provides a tool to initialize audits in low-income settings using the ICD-PM for classifying perinatal deaths. The ICD-PM maps ICD-10 codes

to an underlying fetal cause of antepartum, intrapartum or unknown timing, and a maternal condition; thus, data collection must include timing as well as fetal and a maternal condition. While this approach aims to capture information on stillbirths from low resource settings (either cause and/or associated conditions) the ICD-PM faces challenges due to its ICD-10 provenance, including insufficient differentiation of causes from associated conditions, and insufficient detail on maternal conditions[8]. Conditions noted as Maternal in the ICD-PM include not only fetal underlying causes *(Placenta, cord and membranes)*, but also maternal causes (*Maternal complications of pregnancy*) and maternal associated conditions (*Maternal medical and surgical conditions*). Further, one-fifth of stillbirths in the global category *Unexplained* mapped to ICD-PM *Antepartum asphyxia*. Classifying associated conditions is important, particularly in data poor settings where assigning cause may be difficult. However confusing causes from associated conditions or mechanisms of deaths (antepartum asphyxia) while reducing the number of *Unexplained*, may obscure key areas for prevention. WHO is currently working towards ICD-11 which provides an opportunity to alleviate some of these issues[World Health Organization, #269].

Differences in proportions of causal categories across countries, were likely due to different classification approaches. Codac[19] was the only non-ICD system fully aligned with the ICD-PM. Although Codac has previously been shown to be the best-performing system[45], the majority of stillbirths classified using Codac were mapped to unknown timing and cause within the ICD-PM (data not shown). Codac also resulted in a high proportion of *Unexplained* stillbirths, potentially influenced by the categories included. Moreover, this system was only aligned with nine of the 17 user-identified characteristics for an effective global system. Future enhancements to global classification of stillbirths need to incorporate user-identified characteristics for an effective global system. Further, optimisation of information from data-rich settings to incorporate recent advances in stillbirth aetiology such as the consensus on placental pathology[53], and other detailed laboratory investigations will serve to advance prevention of stillbirths globally. Implementation of any system must also be accompanied by appropriate training to ensure high-quality data.

Conclusion

To achieve the Every Newborn Action Plan global stillbirth rate target, improving care of women in labour and birth and preventing and treating infections and the quality of data on causes to drive change are priorities. Implementation of ICD-PM as part of the WHO Perinatal Mortality Audit and Review guide[7] would be a major step forward. While the ICD-PM captures data from high-burden settings by allowing for a minimum of timing and clinically defined causes and associated conditions, a global system must also accommodate needs of data-rich settings to enable global comparisons. Clearly ascertaining underlying causes separate from associated conditions and enabling capture of more detailed information in data-rich settings will fully harness the ICD-PM's potential for global reporting and prevention of stillbirths. Further research is needed to improve the classification of placental causes of stillbirths. Enhancements to global classification of stillbirths and neonatal deaths must be based on comprehensive testing across diverse settings.

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Disclosure of Interests

GS receives/has received research support from GE (supply of two diagnostic ultrasound systems), from Roche (supply of equipment and reagents for biomarker studies, value £596,142) and from GSK (£199,413 for in vitro studies on human myometrium). GS has been paid to attend advisory boards by GSK and Roche. GS has acted as a paid consultant to GSK. GS has received support to attend a scientific meeting from Chiesi. GS is named inventor in a patent submitted by GSK for a novel

application of an existing GSK compound for the prevention of preterm birth (PCT/EP2014/062602). GS was a member of a GSK Data Safety Monitoring Committee for a trial of RSV vaccination in pregnancy and infancy, 2016-2017.

Contribution to Authorship

HR was responsible for the conduct of the study. VF conceptualized the study and developed methods and procedures with HR, MC and SHL. HR, VF, SHL, AW and ZT undertook searches, selection of studies, data extraction and quality assessment. GG, DE, RL and VF created the global stillbirth categories. MC oversaw all statistical aspects of the study and undertook the pooled analysis. VF and SHL undertook the assessment of ICD-PM alignment with advice from RP, JG, ÖT and EA. HR and VF were responsible for interpretation of findings and preparation of the first draft of the manuscript. SH, AW, GG, RL, DE, ZT, EA, HB, ED, JJE, FF, JG, KG, SG, AG, AH, YK, FK, JL, EM, JO, RP, KP, DS, RS, GS and ÖT have been actively involved throughout planning and consultation stages of the project and provided comments on the manuscript. HR, SHL, MC, SH, AW, GG, RL, DE, ZT, EA, HB, ED, JJE, FF, JG, KG, SG, AG, AH, YK, FK, JL, EM, JO, RP, KP, DS, RS, GS and ÖT approved the final version. All authors are part of The International Stillbirth Alliance Collaborative for Improving Classification of Perinatal Deaths.

Details of Ethics Approvals

Not required

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