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Epidemiology

A prospective cause of death classification system for maternal deaths in low and middle-income countries: results from the Global Network Maternal Newborn Health Registry

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Objective To describe the causes of maternal death in a population-based cohort in six low- and middle-income countries using a standardised, hierarchical, algorithmic cause of death (COD) methodology.

Design A population-based, prospective observational study.

Setting Seven sites in six low- to middle-income countries including the Democratic Republic of the Congo (DRC), Guatemala, India (two sites), Kenya, Pakistan and Zambia.

Population All deaths among pregnant women resident in the study sites from 2014 to December 2016.

Methods For women who died, we used a standardised questionnaire to collect clinical data regarding maternal conditions present during pregnancy and delivery. These data were analysed using a computer-based algorithm to assign cause of maternal death based on the International Classification of Disease—Maternal Mortality system (trauma, termination of pregnancy-related, eclampsia, haemorrhage, pregnancy-related infection and medical conditions). We also compared the COD results to healthcare-provider-assigned maternal COD.

Main outcome measures Assigned causes of maternal mortality.

Results Among 158 205 women, there were 221 maternal deaths. The most common algorithm-assigned maternal COD were obstetric haemorrhage (38.6%), pregnancy-related infection (26.4%) and pre-eclampsia/eclampsia (18.2%). Agreement between algorithm-assigned COD and COD assigned by healthcare providers ranged from 75% for haemorrhage to 25% for medical causes coincident to pregnancy.

Conclusions The major maternal COD in the Global Network sites were haemorrhage, pregnancy-related infection and pre-eclampsia/eclampsia. This system could allow public health programmes in low- and middle-income countries to generate transparent and comparable data for maternal COD across time or regions.

Keywords Cause of death, classification, low- and middle-income countries, maternal mortality.

Tweetable abstract An algorithmic system for determining maternal cause of death in low-resource settings is described.

Linked article This article is commented on by M Mathai, p. 1144 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15145.

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Introduction

Maternal deaths worldwide have fallen from an estimated 532 000 in 1990 to 303 000 in 2015 representing a maternal mortality rate for 2015 of approximately 220/100 000 live births. To reach the World Health Organization's (WHO) Sustainable Development Goal of 70 deaths per 100 000 live births globally by 2030,[1] low- and middle-income countries (LMIC) will have to reduce their maternal mortality rate by 7.5% annually, a rate of reduction currently achieved by only Rwanda, Cambodia and Timor-Leste.[2]

Reliable cause of death (COD) is essential to strategies to avert maternal mortality.[3–5] However, misclassification of maternal COD is widespread, even in countries with complete vital registration.[6–8] In countries with the highest burden of maternal mortality, the lack of COD data is critical. Only one of ten countries with high maternal mortality rate has published maternal COD data.[9]

The standard for assignment of maternal COD is a diagnostic autopsy.[1] However, this procedure is rarely performed where maternal mortality is common.[10] Alternatively, various methods determine maternal COD, ranging from multidisciplinary investigations such as confidential enquiries in the UK[1] to verbal autopsies to identify COD outside health facilities.[11]

There are numerous challenges in each methodology, particularly in LMIC, including identification of maternal deaths, validity of data collection instruments, time required to gather requisite data, reliability of information, capacity of those gathering data and lack of standardisation of classification across methods.[9] Common to all is a concern related to the expert assignment of COD, where, given the same information, various experts may select different causes.[12]

Attempts to improve attribution of maternal mortality have focused on benchmarks for certification of COD by healthcare providers.[13] However, in settings where COD is ascertained by providers untrained in clinical diagnosis, there is little standardisation of methods. To improve consistency, inter-observer agreement and comparability, we developed an algorithm[14] based on the International Classification of Disease—Maternal Mortality (ICD-MM) system, to assign COD. In this system, the causes include trauma, termination of pregnancy-related mortality, pre-eclampsia/eclampsia, haemorrhage, pregnancy-related infection and medical conditions not associated with pregnancy.[15,16] The purpose was to determine maternal COD within the Maternal Newborn Health (MNH) Registry, a population-based cohort of pregnant women of the National Institute of Child Health and Human Development (NICHD)'s Global Network for Women's and Children's Health Research (Global Network). We used an algorithmic classification system to assign COD, and compared the algorithmic-assigned results to the clinically assigned COD by the healthcare attendant.

Methods

The Global Network is a multi-country research network funded through grants from NICHD. The Global Network's MNH Registry is a prospective, active surveillance system developed to track pregnancies and birth outcomes in rural or semi-urban communities in India (two states), Pakistan, Kenya, Democratic Republic of the Congo (DRC), Zambia and Guatemala. Through the Registry, all pregnant women who provide consent and are residents of the catchment areas are followed with outcomes obtained at delivery and at approximately 42 days postpartum. Registry administrators (generally nurses or health workers trained in the study) obtain information about the health of the mother and infant during the antenatal, labour and delivery, and postnatal periods as well as data about maternal and neonatal treatments. For all cases of maternal death, the cause of death assigned by the healthcare provider is recorded. Place of delivery is coded as either home, clinic/health centre or hospital with the latter defined as a facility with physicians in attendance able to provide more advanced emergency obstetric care including caesarean section. Data from all consenting pregnant women are included in the Registry database as described in detail elsewhere.[17,18]

In 2014, a COD form was added to the Registry and staff were trained to collect the additional data (see Appendix S1. Global Network Maternal Cause of Death form). For every woman enrolled in the Registry who died during the study period, a maternal COD form was completed by the trained registry administrators. All women who were eligible for the MNH Registry were screened for inclusion in the analysis and those with a completed COD form were included. The analysis for this study used maternal COD data collected from 2014 (start dates varied by study site) through December 2016.

Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.

The Global Network Maternal Mortality Algorithm (Figure 1) was developed to determine the likely cause of

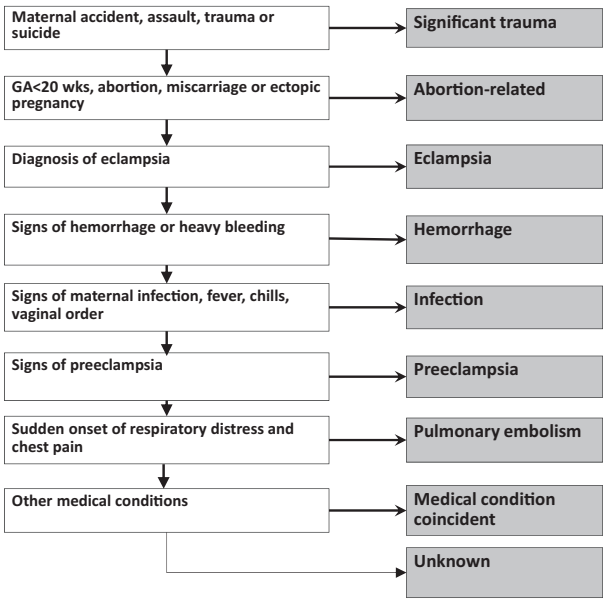

Figure 1. Global Network maternal cause of death algorithm (published with permission).[14]

maternal death in large populations monitored by health workers and to assign COD by algorithm.[14] It first identifies significant maternal trauma and if present, the COD is designated as trauma. If there is no trauma and the pregnancy terminates at <20 weeks, the cause of maternal death is classified as termination of pregnancy-related.

If neither of these conditions is present, and the woman experienced a seizure, eclampsia is considered the COD. If no trauma or seizure occurred in a woman with a pregnancy of >20 weeks of gestation and any signs of haemorrhage are present, haemorrhage is assigned as the COD. In the absence of all preceding symptoms, when signs of pregnancy-related infection are present, infection is assigned as the COD. Other signs of hypertensive disease, and especially pre-eclampsia, are handled in a similar manner. Signs of pulmonary embolism are considered next. Finally, if none of the above are present, the algorithm considers medical conditions not directly associated with the pregnancy, such as renal disease, heart disease, cancer or diabetes, and if any of these are present, the medical condition is assigned as the COD. If none of the above is present, the COD is classified as unknown.[14] For this analysis, eclampsia and pre-eclampsia are considered as a single COD.

Trained staff collected all data on hard copy, which were entered into a dedicated research computer at each study site. Initial quality checks were performed before transmitting data to the central coordinating centre, where additional data-editing checks were performed.

The study was intended to be descriptive and sample size was based on the data available during the 2-year period. Data from all the study sites were combined for the primary analyses. Because the number of deaths by country was generally small, for analyses, we grouped the sites into those in South Asia, those in Africa, and Guatemala, the only Latin American site. All analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

The study was reviewed and approved by the involved institutions' ethics review committees including the committees in the US institutions that partnered with each of the foreign sites. A Data Monitoring Committee appointed by NICHD reviews the Registry data on at least an annual basis. All women reported in this analysis provided consent to participate in the study.

Results

From January 2014 to December 2016 in Equateur, DRC; Belagavi, India; and Thatta, Pakistan, and from July 2014 to December 2016 in Lusaka, Zambia; Chimaltenango, Guatemala; Nagpur, India; and western Kenya (the counties of Busia, Bungoma and Kakamega), a total of 159 309 pregnant women were screened, 526 of those were ineligible, and 158 205 (99.6% of eligible) consented for enrolment in the Registry (Figure 2). A total of 1861 women were lost to follow up before delivery and 392 were

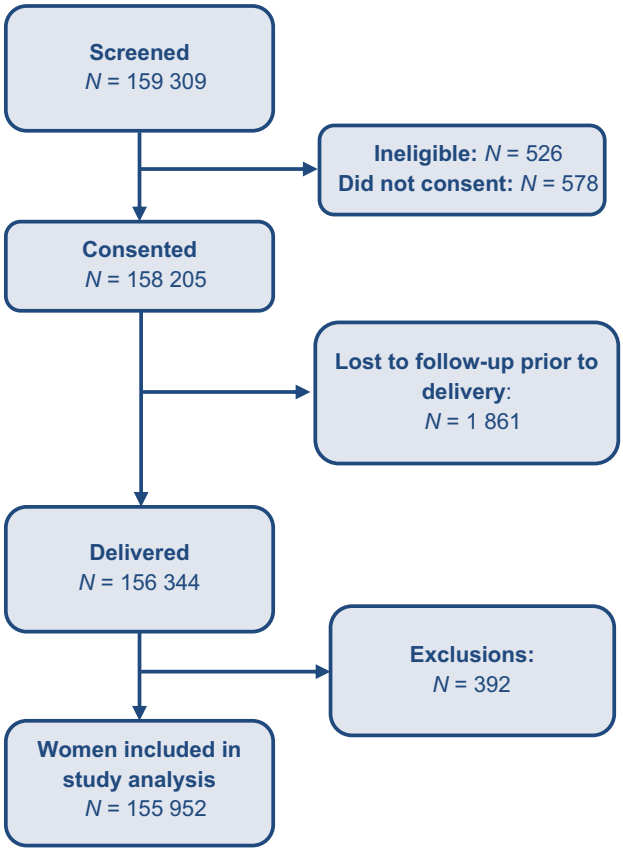

Figure 2. Diagram of study enrolment, 2014–2016.

excluded due to missing delivery data; a total of 155 952 women were available with delivery outcomes.

Table 1 describes the delivery location of the study population. The number of pregnant women evaluated at each site ranged from 16 338 in Lusaka, Zambia to 29 348 in Belagavi, India. Overall, 41.6% women delivered at a hospital, 33.5% in a health clinic and 24.8% at home. The proportion of home births ranged from 4.0% in Nagpur, India to 44.9% in Chimaltenango, Guatemala. The total number of maternal deaths in this cohort was 221, representing a maternal mortality ratio of 153 deaths per 100 000 live births, with considerable variability across the sites. The highest rate of maternal deaths occurred in the sites in Thatta, Pakistan and Equateur, DRC and the lowest in Lusaka, Zambia. Among women delivered at home, 47 deaths occurred (121/100 000), 27 deaths occurred among those delivered at a health centre (52/100 000) and 87 deaths occurred among hospital deliveries (134/100 000). In addition, 59 women died at home before delivery and one was missing the location of death (data not shown).

Across all sites, the three most common causes of maternal death, which accounted for 83% of all mortality, included obstetric haemorrhage (38.6%), pregnancy-related infection (26.4%) and pre-eclampsia/eclampsia (18.2%) (Figure 2). The remaining maternal deaths were attributed to medical conditions (5.5%), trauma (4.5%) and termination of pregnancy-related deaths (2.7%). No deaths were attributed to pulmonary embolism. Four percent of deaths were classified as due to unknown causes.

In the South Asian sites, 78 of the 129 deaths occurred in Thatta, Pakistan (60.9%). The most common cause of maternal death in the region was haemorrhage (49/129; 38.0%), followed by pregnancy-related infection (43/122; 33.3%) and pre-eclampsia/eclampsia (16/122; 12.4%). Despite the wide difference in maternal mortality ratios between the sites in India and Pakistan, the relative distribution of COD was similar in all three South Asian sites with haemorrhage and pregnancy-related infection accounting for two-thirds or more of all deaths (data not shown). Two-thirds of all the deaths in the three sub-Saharan African sites occurred in Equateur, DRC (48/71; 67.7%). The most frequent cause of maternal death in the African sites was haemorrhage (28/71; 39.4%), followed by pre-eclampsia/ eclampsia (16/71; 22.5%) and pregnancy-related infection (12/71; 16.9%). In Guatemala, haemorrhage and eclampsia/pre-eclampsia were both responsible for 40% of the maternal deaths.

We examined the agreement between COD assigned by the algorithm compared with COD assigned by the healthcare provider (Table 2). The highest level of agreement was for death due to haemorrhage. More than 75% of women (65/85) with COD assigned as haemorrhage by the algorithm had the same COD assigned by the healthcare

Table 1. Delivery site and maternal mortality ratios by site

	Total	Equateur, DRC	Lusaka, Zambia	Chimaltenango, Guatemala	Belagavi, India	Thatta, Pakistan	Nagpur, India	Western Kenya
Deliveries, *n*	155 952	16 966	16 210	24 997	29 332	28 321	22 951	17 175
Delivery location, *n* (%)								
Hospital	64 905 (41.6)	1573 (9.3)	3898 (24.1)	13 567 (54.3)	15 569 (53.1)	9761 (34.5)	16 573 (72.2)	3964 (23.1)
Clinic or health centre	52 260 (33.5)	11 072 (65.3)	9417 (58.1)	198 (0.8)	9893 (33.7)	7611 (26.9)	5459 (23.8)	8610 (50.2)
Home/Other	38 727 (24.8)	4311 (25.4)	2891 (17.8)	11 230 (44.9)	3864 (13.2)	10 929 (38.6)	910 (4.0)	4592 (26.8)
42-day maternal mortality ratio, *n/N* (rate/100 000 live births)	221/14 4489 (153)	48/16 431 (292)	11/16 073 (68)	20/24 486 (82)	25/24 842 (101)	78/24 470 (319)	26/21 254 (122)	13/16 933 (77)

Table 2. Comparison between cause of death assigned by algorithm and cause of death assigned by clinician

	Cause of maternal death assigned by algorithm						
	Haemorrhage	Infection	Pre-eclampsia/ eclampsia	Medical condition	Trauma	termination of pregnancy-related	Unknown
Clinically assigned cause of maternal death, *n* (%)	85	58	40	12	10	6	9
Haemorrhage	65 (76.5)	1 (1.7)	3 (7.5)	1 (8.3)	0 (0.0)	2 (33.3)	0 (0.0)
Infection	8 (9.4)	21 (36.2)	4 (10.0)	1 (8.3)	0 (0.0)	1 (16.7)	0 (0.0)
Pre-eclampsia/eclampsia	2 (2.4)	6 (10.3)	25 (62.5)	0 (0.0)	2 (20.0)	0 (0.0)	3 (33.3)
Obstructed/prolonged labour	3 (3.5)	4 (6.9)	1 (2.5)	2 (16.7)	0 (0.0)	0 (0.0)	2 (22.2)
Trauma	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	6 (60.0)	0 (0.0)	0 (0.0)
termination of pregnancy-related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)
Anaemia	4 (4.7)	13 (22.4)	1 (2.5)	4 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other medical condition	1 (1.2)	10 (17.2)	2 (5.0)	3 (25.0)	0 (0.0)	0 (0.0)	1 (11.1)
Other*	2 (2.4)	3 (5.2)	4 (10.0)	0 (0.0)	2 (20.0)	1 (16.7)	3 (33.3)

*Other = Poisoning with traditional herbs, witchcraft, complications of medical treatment, shortness of breath, renal failure, sudden death.
Grey shaded box indicated agreement between clinical and algorithm assigned cause of death.

providers. Pre-eclampsia/eclampsia also had reasonable agreement between the algorithm and healthcare providers; 25 of the 40 deaths (62.5%) classified as being due to pre-eclampsia/eclampsia by the algorithm were similarly classified by healthcare providers. Pregnancy-related infection had the greatest disparity between assignment by algorithm and healthcare providers; <40% of the deaths assigned to pregnancy-related infection using the algorithm were also classified as infection by clinicians (21/58; 36.2%). Among the remainder of COD assigned by the algorithm, agreement with healthcare providers for deaths due to trauma was 60% (6/10) and 33% (2/6) for termination of pregnancy. Among deaths due to medical causes coincident to pregnancy by the algorithm, the COD for 25% (3/12) was assigned as anaemia by healthcare providers. The algorithm, in line with the WHO guidelines, does not assign anaemia as a specific primary cause of maternal death. However, in 22 of the 221 (10%) maternal deaths, the primary COD assigned by the attending healthcare provider was anaemia.

We also examined the treatment received by the mother before death (Table 3). Of the deaths attributed to haemorrhage, 72.4% received oxytocin/misoprostol, and only 40.8% received a blood transfusion. Of the deaths attributed to pre-eclampsia/eclampsia, 37.5% received magnesium sulphate and of the deaths attributed to pregnancy-related infection, 59.0% of the women received antibiotics. Of the six deaths attributed to a termination of pregnancy, only two received a dilation and curettage and one received a hysterectomy.

Table 3. Care received by maternal cause of death assigned by algorithm

Maternal treatment received	Cause of maternal death assigned by algorithm						
	Haemorrhage	Infection	Pre-eclampsia/ eclampsia	Medical condition	Trauma	Termination of pregnancy-related	Unknown
Maternal deaths <42 days, *n*	85	58	40	12	10	6	9
Caesarean section	21 (27.6)	10 (25.6)	13 (52.0)	3 (37.5)	1 (100.0)	0 (0.0)	2 (28.6)
Antibiotics	41 (55.4)	23 (59.0)	14 (58.3)	5 (62.5)	1 (100.0)	5 (83.3)	4 (57.1)
Oxytocin or misoprostol	55 (72.4)	21 (53.8)	15 (65.2)	5 (62.5)	1 (100.0)	3 (50.0)	4 (57.1)
Blood transfusion	31 (40.8)	12 (30.8)	7 (28.0)	5 (62.5)	0 (0.0)	1 (16.7)	2 (28.6)
Dilation and curettage or suction	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)
Magnesium sulphate	1 (1.3)	0 (0.0)	9 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)
Hysterectomy	3 (3.9)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)

Discussion

Main findings

Using the Global Network Maternal Mortality Algorithm, we found that the major causes of death were obstetric haemorrhage (35.4%), pregnancy-related infection (28.6%) and pre-eclampsia/eclampsia (19.0%). Termination of pregnancy was limited to 3% of the deaths, probably because most were enrolled after 20 weeks of gestation, although sites attempted to identify all maternal deaths that occurred during the study period.

In sub-Saharan Africa, one-third of deaths were attributed to haemorrhage, and pregnancy-related infection and pre-eclampsia/eclampsia each accounted for one-quarter of deaths. In South Asia, haemorrhage and pregnancy-related infection each accounted for one-third of mortality and pre-eclampsia/eclampsia for only 12.5% of the deaths. In Guatemala, 40% deaths were due to pre-eclampsia/eclampsia, 40% due to haemorrhage and 15% due to pregnancy-related infection. High maternal mortality in Latin America from hypertensive diseases has been reported.[19]

Comparing the COD using the algorithm with the healthcare provider also provides insight into challenges for provider-assigned COD. For haemorrhage or pre-eclampsia/eclampsia, the healthcare provider assigned the same COD as the algorithm for 75% of cases. On the other hand, when the algorithm identified pregnancy-related infection, providers concurred less than half of the time. More than 10% of the deaths were attributed to anaemia by providers, whereas the algorithm grouped anaemia under other conditions.

Finally, comparing COD with treatments received was illuminating. For the major causes, standard beneficial treatment was not given for a substantial proportion of women. Although more definitive research on this is needed, these results suggest that many deaths may have been preventable. An important quality-of-care measure is whether appropriate treatment was available and ultimately used.

Strengths and limitations

This is one of the largest prospective, population-based causes of maternal mortality studies in LMIC and the study was conducted in a diverse range of study sites in sub-Saharan Africa, South Asia and Guatemala. However, although this is one of the largest maternal mortality studies, the total number of deaths was relatively small with the majority occurring in Thatta, Pakistan and Equateur, DRC.

One of the study's limitations was that the COD was not validated using methods such as diagnostic autopsy. Additionally, the Registry focused on enrolment at 20 weeks of gestation, which precluded accurate assessment of termination of pregnancy-related deaths.

Although the Global Network Maternal Mortality Algorithm generally aligns with the WHO classification system, it is necessarily a simplification and causes such as pulmonary embolism were probably under-detected in low-resource settings. To align with WHO, we did not designate anaemia as a COD, which may underemphasise its contribution to mortality in South Asia where severe maternal anaemia is common.[20,21] Additionally, obstructed labour was not a COD, consistent with WHO, rather obstructed labour-related deaths were generally attributed to infection or haemorrhage.

Interpretation

Reviewing 60 000 maternal deaths from various studies, Say et al.[9] found that haemorrhage (27%), hypertensive disorders (14%) and sepsis (11%) were the most common causes. In our study, the three same causes of death predominated across all sites. Interestingly, the most common cause of maternal death in each of the three Global Network regions: haemorrhage in sub-Saharan Africa, hypertensive disorders in Latin America and pregnancy-related infection in South Asia, was also the most common cause in these regions in Say et al.'s review.

Maternal mortality remains one of the most inequitable health outcomes between well-resourced and poorly resourced settings.[22,23] Interventions, such as increasing skilled birth attendants for delivery, have not delivered optimal outcomes across all settings. As in the Global Network, many maternal deaths now occur among women delivering at facilities, often because women with obstetric complications reach facilities too late, the facilities are poorly equipped or because of inappropriate care.

Reliable assignment of COD remains a challenge, as evidenced by the fact that multiple clinical providers with the same information will assign different COD.[12] This is compounded by the absence of COD training and limited clinical investigations often found in LMIC.

Conclusions

The Global Network Maternal Mortality Algorithm describes a methodology using basic investigations, observation, or interview with the mother, lay-health provider or family to inform COD. The algorithmic approach is consistent, reproducible, and comparable over time and across geographical locations, and has data requirements that are realistic for the settings where most maternal deaths occur.

Disclosure of interest

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

The study protocol was developed by OP, EMM, SS, AL, AT, CLB, MB, EC, WAC, ALG, KMH, NFK, SG, BK, RJD, AP, PLH, FE, EAL, JLM, DDW, MKT, MM and RLG. The

study was implemented by SST, AL, MM, LF, AP, CT, SD, with oversight by SS, AT, EC, ALG, SG, and OP. JLM, EMM and DDW conducted the statistical analysis. OP wrote the first draft of the manuscript with RLG and EMM. Additional reviews provided by SS, AL, AT, CLB, MB, EC, WAC, ALG, KMH, NFK, SG, BK, RJD, AP, PLH, FE, EAL, JLM, DDW, MKT, MM. All authors reviewed approved the final draft of the manuscript.

Details of ethics approvals

The study was approved by the ethics review committee of participating institutions in 2013 before study initiation (Universite de Kinshasa, Ecole de Sante Publique, DRC; University of Zambia, Zambia; Instituto de Nutrición de Centro América y Panamá, Guatemala City; KLE University's JN Medical College, Belagavi, India; Lata Medical Research Foundation, Nagpur, India; Aga Khan University, Pakistan; Moi University, Kenya) and their US partner IRBs (University of North Carolina at Chapel Hill; University of Alabama at Birmingham; University of Colorado Denver; Thomas Jefferson University; Columbia University; Indiana University, Boston University). In addition, approval was obtained by the data coordinating centre at RTI International.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Maternal cause of death data form. ■

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