Incidence and characteristics of pregnancy-related death across ten low- and middle-income geographical regions: secondary analysis of a cluster randomised controlled trial

N Vousden,[a] E Holmes,[a] PT Seed,[a] MF Gidiri,[b] S Goudar,[c] J Sandall,[a] S Chinkoyo,[d] LY Kumsa,[e,f] A Brown,[e,f] U Charantimath,[c] M Bellad,[c] A Nakimuli,[g] B Vwalika,[h] LC Chappell,[a] AH Shennan,[a] on behalf of the CRADLE Trial Collaborative Group[†]

[a] Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK [b] Department of Obstetrics and Gynaecology, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe [c] Women's and Children's Health Research Unit, KLE Academy of Higher Education and Research Jawaharlal Nehru Medical College, Belgaum, Karnataka, India [d] Department of Obstetrics and Gynaecology, Ndola Teaching Hospital, Ndola, Zambia [e] Maternity Worldwide, Brighton, UK [f] Maternity Worldwide, Addis Ababa, Ethiopia [g] Department of Obstetrics and Gynaecology, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda [h] Department of Obstetrics and Gynaecology, University of Zambia School of Medicine, Lusaka, Zambia

Correspondence: N Vousden, Department of Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, SE1 7EH, UK. Email: Nicola.vousden@kcl.ac.uk

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Objective The aim of this article is to describe the incidence and characteristics of pregnancy-related death in low- and middle-resource settings, in relation to the availability of key obstetric resources.

Design This is a secondary analysis of a stepped-wedge cluster randomised controlled trial.

Setting This trial was undertaken at ten sites across eight low- and middle-income countries in sub-Saharan Africa, India and Haiti.

Population Institutional-level consent was obtained and all women presenting for maternity care were eligible for inclusion.

Methods Pregnancy-related deaths were collected prospectively from routine data sources and active case searching.

Main outcome measures Pregnancy-related death, place, timing and age of maternal death, and neonatal outcomes in women with this outcome.

Results Over 20 months, in 536 233 deliveries there were 998 maternal deaths (18.6/10 000, range 28/10 000–630/10 000). The leading causes of death were obstetric haemorrhage (36.0%, n = 359), hypertensive disorders of pregnancy (20.6%, n = 206), sepsis (14.1%, n = 141) and other (26.5%, n = 264). Approximately a quarter of deaths occurred prior to delivery (28.4%, n = 283), 35.7% (n = 356) occurred on the day of delivery and 35.9% (n = 359) occurred after delivery. Half of maternal deaths (50.6%; n = 505) occurred in women aged 20–29 years, 10.3% (n = 103) occurred in women aged under 20 years, 34.5% (n = 344) occurred in women aged 30–39 years and 4.6% (n = 46) occurred in women aged ≥40 years. There was no measured association between the availability of key obstetric resources and the rate of pregnancy-related death.

Conclusions The large variation in the rate of pregnancy-related death, irrespective of resource availability, emphasises that inequality and inequity in health care persists.

Keywords Epidemiology, low and middle resource, maternal mortality.

Tweetable abstract Inequality and inequity in pregnancy-related death persists globally, irrespective of resource availability.

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Introduction

In 2017, an estimated 295 000 women died as a result of pregnancy and childbirth. There are stark inequalities in the risk of death worldwide, where the lifetime risk of maternal mortality in sub-Saharan Africa is 1 in 37, compared with 1 in 4800 in Europe and Northern America.[1]

There are methodological challenges with measuring maternal death. Many countries with the highest rates of maternal death lack comprehensive civil registration systems and accurate reporting, and therefore pose a major challenge. Classification of the cause of death is also challenging, especially where the certification of death is not formalised.[2] Even when a civil registration system exists, in the absence of active case finding, maternal deaths may be misclassified and the use of diverse sources, including household surveys, censuses and verbal autopsies, limits comparisons of maternal mortality worldwide.[1] International comparisons are therefore usually based on modelled estimates.[1] For some countries these are given with wide ranges (e.g. in Sierra Leone, 808–1620/100 000 births), showing the absence of reliable, prospective data in these countries.

The leading causes of maternal death worldwide are haemorrhage (27%), hypertensive disorders of pregnancy (14%) and sepsis (11%).[3] These proportions vary by region: for example, hypertensive disorders contribute to a greater proportion of deaths in Latin America and the Caribbean (22.1%), compared with sub-Saharan Africa (16.0%).[3] A review of 14, predominantly small, regional studies, concluded that the majority of maternal deaths occur in hospital (from 40% in Vietnam to 92% in South Africa).[4] The proportion varied greatly depending on the country and the data collection method, where capturing deaths in the community can be challenging. Data modelled from a variety of sources estimate that globally, a quarter of deaths occur antepartum (24.6%), slightly over a quarter occur intrapartum or within 24 hours of delivery (27.7%), a third occur within 42 days of delivery (35.6%) and a minority occur later than this.[5] The lack of reliable country-specific data is important in research and policy, as it is not clear where interventions should be targeted to have the greatest impact on mortality.

The aim of this article is to describe the accurate incidence (per 10 000 deliveries) and characteristics of pregnancy-related death (defined as all deaths that occur in pregnancy and up to 42 days after delivery, irrespective of cause[6]) across ten geographical regions, collected prospectively in eight low- and middle-income countries in relation to key obstetric resources. The secondary aim is to describe the effect of novel vital sign device and educational package on pregnancy-related death.

Methods

This is a secondary analysis of a pragmatic, stepped-wedge cluster randomised controlled trial of the introduction of the Community Blood Pressure Monitoring in Rural Africa: Detection of Underlying Pre-Eclampsia (CRADLE) intervention into routine maternity care in ten regions across Zimbabwe, Zambia, Sierra Leone, Malawi, Ethiopia, Uganda, Haiti and India over 20 months, from 1 April 2016 to 30 November 2017 (International Standard Randomised Controlled Trial Number, ISCRTN: 41244132).[7,8] The CRADLE intervention consisted of the CRADLE Vital Sign Alert,[7,9] a validated device that accurately measures blood pressure (BP) and heart rate and calculates the shock index, displaying the results on a traffic light early warning system, and a simple education package on how to use the device and respond to abnormal vital signs.[10,11] This intervention was compared with routine maternity care using local management guidelines.

Each region comprised at least one secondary or tertiary health facility that provided comprehensive emergency obstetric care with the main peripheral facilities that refer to these hospitals. All secondary or tertiary hospitals were urban or peri-urban, but the geographical regions of peripheral facilities covered a range of settings, with the mean distance varying from 3.3 to 74.0 km to the referral centre. Community healthcare providers were included, when they were formally involved in routine maternity care provision and supported at the district level.[7] The intervention was delivered to all healthcare professionals (HCPs) working in gynaecology and maternity in the facilities of the region.

Core outcomes

The primary outcome of the trial was a composite outcome of maternal mortality and morbidity (at least one of eclampsia, emergency obstetric hysterectomy and maternal death). In spite of a 9% reduction in the primary outcome over time, the trial was unable to demonstrate an effect of the intervention as a result of the unexpected degree of variation between and within regions. All women that were recorded as having died at any gestation or up to 42 days after delivery, from any cause, between 1 April 2016 and 31 November 2017 were eligible for inclusion as a pregnancy-related death case in this secondary analysis. The denominator was all deliveries in the trial area in the same period. For each woman, data were collected on the cause of death, maternal age, timing and place of pregnancy-related death (community, peripheral facility or central referral facility). The number of stillbirths and neonatal deaths up to 28 days was recorded in all women that died. These outcomes were selected as they are of great clinical importance; no core outcome set was available.

Regions were described by the number of deliveries, number of HCPs working in maternity, the number of intensive care unit (ICU) beds per 1000 deliveries and the proportion of facilities where blood transfusion was available on a monthly basis. Methods of data collection were discussed and optimised based on the existing resources available in each region. All data collectors were given detailed training to ensure the comparability of results. Outcomes were triangulated across multiple sources depending on the reliability in each region (including referral registers, ward registers, patient records, local mortality and morbidity records, and active case searching) to ensure data completeness, and all outcomes were checked to avoid double counting. The systematic reporting of community cases, for example through household surveys, was not undertaken. Therefore, community cases are included where reported, and in these predominantly urban settings, we consider that most community deaths were made known to our researchers. All data were entered onto a standardised electronic central database. Where possible, cause of death was attributed to the highest-level cause in keeping with the WHO guidance on cause of death.[12]

Ethics, consent and patient involvement

Ethical approval was granted by the Biomedical Sciences, Dentistry, Medicine and Natural and Mathematical Sciences Research Ethics Subcommittee at King's College London (LRS-14/15-1484) and at each study centre (excluding Haiti, for which Memorandum of Understandings were created because of the lack of existing process). This and all local ethical approvals were in place prior to the start of the study. Institutional-level consent on behalf of the cluster was obtained. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Statistical methods and analysis

Statistical analyses were undertaken in STATA 13.1 (Stata-Corp LLC, College Station, TX, USA). We used logistic regression on monthly data with standard errors corrected for clustering by centre ID, and with no fixed effect of centre.[13] Results are reported as odds ratios (ORs) with 95% confidence intervals. The trial protocol stated that further details of the individual components of the primary outcome would be analysed, such as cause and place of death.[7] To describe the association between death and resource availability, pregnancy-related death rates for each centre and time period (month) were calculated. The correlation of ICU bed availability (average per 10 000 deliveries), blood transfusion availability (mean percentage of facilities) and HCPs (average per 1000 deliveries) with maternal death by region used linear regression for the log of pregnancy-related death rate, with robust standard errors.

Analyses were corrected for clustering by centre with no fixed effects. Individual patient data were only collected for known cases.

Results

In this cohort of 536 233 deliveries there were 998 pregnancy-related deaths over 20 months. This gives an overall incidence of 0.19 (18.6/10 000 deliveries); however, the rates of mortality varied substantially between regions, as shown in Table 1 (ranging from 2.8/10 000 in Zambia Centre 1 to 63.0/10 000 in Sierra Leone).

The overall leading causes of mortality were obstetric haemorrhage (36.0%, $n = 359$), hypertensive disorders of pregnancy (20.6%, $n = 206$), sepsis (14.1%, $n = 141$) and other (26.5%, $n = 264$), with the causes included in 'other' each representing individual contributions of less than 4%. The causes of death categorised as other included anaemia (3.4%, $n = 34$), early pregnancy complications (3.0%, $n = 30$) and malaria (2.3%, $n = 23$). The proportions varied between regions, as shown in Table S1 (obstetric haemorrhage, ranging from 15.2% in India to 44.5% in Uganda Centre 1; sepsis, ranging from 0.0% in Haiti to 27.5% in Zimbabwe; hypertensive disorders of pregnancy, ranging from 9.9% in Zambia Centre 2 to 68.0% in Haiti). After planned adjustments for clustering and time trends in each region, the implementation of the CRADLE intervention was not associated with any significant change in the rates of death from any cause, although unexpected variability between regions and over time meant that we could not rule out an effect (Table 2).

Half of pregnancy-related deaths (50.6%, $n = 505$) occurred in women aged 20–29 years, 10.3% ($n = 103$) occurred in women aged under 20 years, 34.5% ($n = 344$) occurred in women aged 30–39 years and 4.6% ($n = 46$) occurred in women aged ≥40 years. The variation in age at death between regions is shown in Figure 1 and Table S2. Slightly over a quarter of deaths occurred prior to delivery (28.4%, $n = 283$), with similar proportions occurring on the day of delivery (35.7%, $n = 356$) and after delivery (35.9%; $n = 359$). Of the deaths that occurred after delivery, the majority were within the first 7 days after delivery (24.8%, $n = 248$), with a further 11.1% ($n = 111$) occurring more than 7 days after delivery (Figure 2; Table S2). Across all study regions, only 1.8% ($n = 18$) of deaths were reported to have occurred in the community (Table S3).

Overall, 715 women died after delivery, of which 46.9% ($n = 335$) had been delivered by caesarean section (ranging from 38.3% in Uganda Centre 2 to 65.2% in Haiti; Table S4). Nearly half of women who died after delivery suffered a stillbirth or a neonatal death (42.5%; $n = 310$), which ranged from 29.2% in Malawi to 48.5% in Sierra Leone (Table S4).

Table 1. Maternal death per 10 000 deliveries, by region and by intervention

Region		Overall	Pre-intervention	Post-intervention
Ethiopia	Rate per 10 000 deliveries	13.3	13.1	13.6
	n/N	47/35 429	32/24 390	15/11 039
Haiti	Rate per 10 000 deliveries	16.8	7.82	26.2
	n/N	25/14 910	6/7670	19/7240
Sierra Leone	Rate per 10 000 deliveries	63.0	142	55.3
	n/N	150/23 806	30/2106	120/21 700
India	Rate per 10 000 deliveries	14.4	14.7	14.1
	n/N	33/22 876	17/11 531	16/11 345
Malawi	Rate per 10 000 deliveries	23.5	24.3	20.8
	n/N	146/62 165	117/48 243	29/13 922
Uganda Centre 1	Rate per 10 000 deliveries	25.7	28.9	24.9
	n/N	328/127 817	72/24 886	256/102 931
Uganda Centre 2	Rate per 10 000 deliveries	10.2	9.7	11.1
	n/N	62/60 502	36/37 003	26/23 499
Zambia Centre 1	Rate per 10 000 deliveries	2.8	6.4	0.5
	n/N	35/123 476	31/48 252	4/75 224
Zambia Centre 2	Rate per 10 000 deliveries	30.1	27.6	31.3
	n/N	81/26 869	23/8343	58/18 526
Zimbabwe	Rate per 10 000 deliveries	23.7	25	11.2
	n/N	91/38 383	87/34 814	4/3569
All regions	Rate per 10 000 deliveries	18.6	18.2	18.9
	n/N	998/536 233	451/247 238	547/288 995

Table 2. Cause of death (% of all deaths)

		Overall	Pre-intervention	Post-intervention	Adjusted comparison OR (95% CI)
Obstetric haemorrhage	Rate per 10 000 deliveries n (%)	6.7 359 (36.0)	5.9 147 (32.6)	7.3 212 (38.8)	OR 0.86 (0.56–1.33)
Pregnancy-related sepsis	Rate per 10 000 deliveries n (%)	2.6 141 (14.1)	2.7 67 (14.9)	2.6 74 (13.6)	–*
Hypertensive disorder in pregnancy**	Rate per 10 000 deliveries n (%)	3.8 206 (20.6)	3.3 81 (18.0)	4.3 125 (22.9)	OR 0.76 (0.46–1.25)
Other	Rate per 10 000 deliveries n (%)	5.4 292 (29.3)	5.7 156 (34.6)	4.3 136 (24.9)	OR 0.88 (0.62–1.24)
All maternal death	Rate per 10 000 deliveries n/N	18.6 998/ 536 233	18.2 451/247 238	18.9 547/288 995	OR 0.79 (0.30–2.09)

*Analysis did not converge.
**Eclampsia, pre-eclampsia or stroke.

Overall, the number of HCPs working in maternity services was 282 per 1000 deliveries. This ranged from 125 per 1000 deliveries in Zambia Centre 1 to 374.3 per 1000 deliveries in Sierra Leone (Table S5). There was no detectable association between the total number of HCPs available and the rates of pregnancy-related death in each region (OR 1.00, 95% CI 1.00–1.01). Two regions, Sierra Leone and Uganda Centre 2, did not have any ICU facility
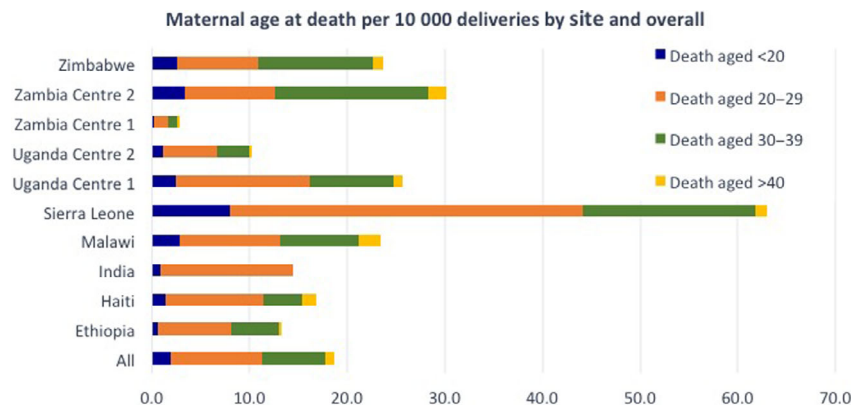
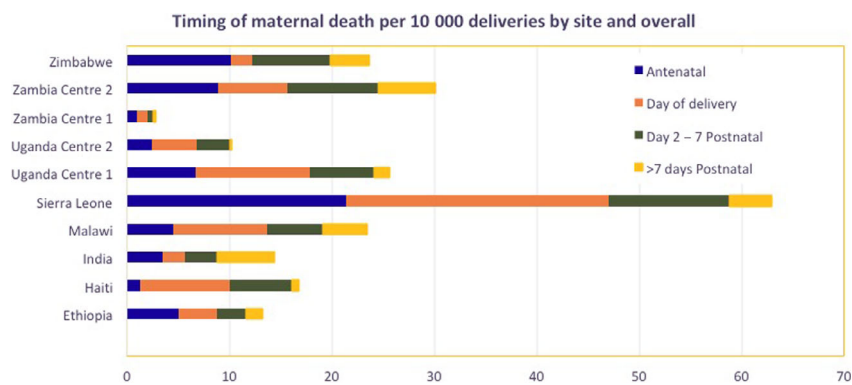**Figure 1.** Maternal age at death per 10 000 deliveries, by region and overall.

Figure 2. Timing of maternal death per 10 000 deliveries, by region and overall.

available. The number of ICU beds per 1000 deliveries in the other regions ranged from 0.8 per 1000 deliveries in Haiti to 24.5 per 1000 deliveries in India. There was also no detectable association between the number of ICU beds per 1000 deliveries and the rates of pregnancy-related death in each region (0 beds, OR 0.69, 95% CI 0.18–2.63; 1–5 beds/1000 deliveries, OR 132, 95% CI 0.49–3.69; 6–10 beds per 1000 deliveries, OR 0.65, 95% CI 0.34–1.23). On average, blood transfusion was available in 25.1% of facilities (ranging from 6.5% in Zambia Centre 2 to 75% in Malawi). There was no evidence of a significant association between the overall availability of blood transfusion and the rate of pregnancy-related death in that region (OR 1.00, 95% CI 0.98–1.03; Table S5).

Discussion

Main findings

Overall, we have found the pregnancy-related death rate to be 18.6/10 000 deliveries, with large variation across individual regions. The leading causes of death were obstetric haemorrhage (36.0%), hypertensive disorders of pregnancy (20.6%), sepsis (14.1%) and other (26.5%). The majority of deaths across all regions occurred in healthcare facilities (98.1%), after delivery (35.9%) and in women aged 20–29 years (50.6%). Overall, the implementation of the CRADLE intervention was not associated with any significant change in the rates of pregnancy-related death, but the effect varied across individual sites. We did not identify any significant association between the measured availability of key obstetric resources and pregnancy-related death rates.

Strengths and limitations

The strengths of this study are the rigorous prospective data collection methods, verified from multiple sources, and the inclusion of multiple settings. Existing prospective data sets are frequently small and are measured at hospital level, with limited information on the place or timing of death. The data presented here improve the accuracy of incidence estimates by reporting these factors and including cases across the health system, including cases from primary healthcare facilities and community cases.

The data were collected during a randomised controlled trial and therefore include measurements before and after the introduction of the intervention, with the included regions selected for research purposes. Although the geographical settings varied, it is a limitation of this study that the majority were urban or peri-urban and may not be representative of nationwide mortality rates. The incidences of mortality reported in this study are lower than recent modelled estimates in all countries except India.[1] This may be representative of the urban settings,[4] or could indicate the underreporting of community cases, as systematic community collection was beyond the capacity of this study. These factors may also explain the lower proportion of deaths reported in the community compared with the literature.[4]

As a result of the study size, it was not feasible to collect demographic data in the denominator group, and therefore the proportion of deaths in different age groups cannot be presented at population level. The cause of death was based on data reported by attending clinicians and other documented or observed factors, as determined by our trained research team. Attributing cause of death was challenging in all regions, because of complex and late presentations to hospital and poor documentation; however, we have demonstrated that the collection of maternal mortality data and entry onto a standardised electronic database is feasible across ten sites with varying infrastructure. It is a strength that this paper reports resource availability, but the daily fluctuations in resource availability remain unknown. The number of HCPs working in maternity facilities was higher than anticipated.[14] This may be linked to the inclusion of untrained support staff or employed staff not regularly working, and therefore might not be a true reflection of the coverage of trained staff providing high-quality care.

Interpretation (in light of other evidence)

In the post-Millennium Development Goal era, the global health focus is on not just reducing mortality but also reducing morbidity.[15] Yet in this study more than 20-fold variation in mortality was observed between regions, suggesting that the focus on maternal mortality globally should not be lost.

In this study, the proportion of deaths from hypertensive disorders of pregnancy was higher than previously cited (20.6% reported compared with 14.0% worldwide and 16.0% in sub-Saharan Africa, where 94.2% of the deaths in our study occurred). This may relate to improved case acquisition after the introduction of the intervention, resulting in the increased reporting of deaths from hypertensive disorder of pregnancy, or the necessity for the research team to record a single leading cause of death (e.g. hypertensive disorder of pregnancy instead of disseminated intravascular coagulation). This highlights the challenges of recording maternal mortality worldwide, despite

guidance from the WHO.[12] Even physician-certified death may be complex because of limited diagnostic services and late presentation at the facility. Continued training and development of local policy in registering maternal deaths is required to ensure the accuracy and comparability of the data, which in turn is vital to inform practice.

Our data suggest that the vast majority of deaths occurred in hospital, despite relatively good availability of resources, probably through a combination of women who arrive too unwell to benefit from emergency care, women with complications who could have been treated with timely effective interventions and women who develop serious complications whilst in hospital. Deaths from women arriving seriously unwell indicate that delays were experienced in deciding to seek and reach care, suggesting a continued need to focus on health system and community factors, such as referral pathways and transport. Importantly, high-quality care within health facilities is required to reduce all causes of maternal deaths.[16] Evidence from low-income countries suggests that increasing the rate of deliveries that occur in facilities does not necessarily equate to improved maternal or neonatal outcomes, because of the poor quality of care, which is estimated to contribute to half of all maternal deaths.[17] Policymakers must therefore address both coverage and service quality to achieve improvements in maternal health.

In keeping with the literature,[4] over a third of women died on the day of delivery (35.7%) and the majority died from obstetric haemorrhage (36.0%). The WHO makes 32 evidence-based recommendations for the prevention and treatment of postpartum haemorrhage.[18] Therefore, HCPs and policymakers have the opportunity to target interventions to this high-risk period, focusing on access and the timely delivery of proven, effective interventions.

In this study, the majority of deaths occurred in women aged 20–29 years, probably reflecting the greatest proportion of births occurring in this group as opposed to a greater relative risk. Nearly half of maternal deaths occurred in women who delivered by caesarean section (45.9%). This is higher than a recent systematic review, in which a quarter of all women who died in low- and middle-income countries (LMICs) had undergone caesarean section (23.8%, 95% CI 21.0–26.7),[19] possibly reflecting the urban setting of our study. The elevated proportion of caesarean sections in this group is likely to indicate severe morbidity necessitating the rapid delivery of the baby; however, it may also add to the literature that mortality risk is disproportionately high following caesarean section in LMICs.[19] This is likely to be of increasing future importance as rates of caesarean delivery increase globally.[20] HCPs and policymakers need to address access to surgery and navigate the challenging balance of under- and overuse of delivery by caesarean section,[21] alongside appropriate decision making for caesarean

sections, such as adequate training and supervision to manage labour and its complications.

We hypothesised that the introduction of the intervention would improve the efficiency and capacity of HCPs to identify, escalate and manage pregnancy complications by increasing the availability of equipment and improving understanding through training and the traffic light early warning system. Although this study has shown no effect of the CRADLE intervention on maternal death, there were trends towards reduced mortality overall and reduced mortality from haemorrhage, sepsis and pregnancy-associated hypertension. Given that this study was not powered to detect differences in individual components of the primary outcome, and had unexpected variation across regions, this warrants further research.

The effect of the intervention differed across regions. It is possible that differing provision of community care, acceptability and infrastructure to facilitate timely referral, and capacity of facilities to provide high-quality, timely care in response to deteriorating vital signs, may all contribute to these differences. Interpretation is challenging, however, as individual sites may be influenced by changes in mortality rates over time, irrespective of the introduction of the intervention, and therefore we considered that this analysis may be misleading.

Conclusion

In conclusion, this analysis provides accurate contemporaneous estimates of incidence of pregnancy-related death from a large prospective data set across eight low- and middle-resource settings. These data highlight that mortality (for the woman and the baby) remains high, with pregnancy and the perinatal period needing continued prioritisation in research and policy. The high proportion of mortality in facility settings indicates that the quality of care and delivery of effective interventions, in addition to timely access to care, is vital. Significant variation across regions and countries, unrelated to staffing levels and interventions, requires an evaluation to define the components that need to be focused on in order to reduce mortality.

Disclosure of interests

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Contribution to authorship

NV, PTS, LCC and AHS designed this study. NV, EH, MFG, SG, SC, LYK, AB, UC, MB, AN and BV contributed

to the acquisition of data. NV, PTS, JS, LCC and AHS contributed to analysis and interpretation of the data. All authors were responsible for drafting the article and for developing the intellectual content.

Details of ethics approval

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Cause of death, by region and overall.

Table S2. Characteristics of maternal death, by region and overall.

Table S3. Place of maternal death, by region (% of all deaths).

Table S4. Perinatal outcomes in women that died after delivery, by region.

Table S5. Availability of key obstetric resources in relation to rates of maternal death. ∎

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