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

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Short Title: Incidence of maternal death in low and middle-income regions

ABSTRACT

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

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

Setting: This trial was undertaken in 10 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 prospectively collected from routine data sources and active case finding.

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% on the day of delivery (n=356) and 35.9% after delivery (n=359). Half of maternal deaths (50.6%; n=505) occurred in women aged 20-29, 10.3% under 20 years (n=103), 34.5% aged 30-39 (n=344) and 4.6% (n=46) aged ≥40. There was no measured association between availability of key obstetric resources and the rate of pregnancy-related death.

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

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Keywords: Maternal mortality, low and middle resource, epidemiology

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

INTRODUCTION

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

There are methodological challenges with measuring maternal death. Many countries with the highest rates lack comprehensive civil registration systems and accurate reporting therefore posing a major challenge. Classification of the cause of death is also challenging, especially where certification of death is not formalized.[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. Sierra Leone from 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 in Latin America and the Caribbean (22.1%) compared to 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 country and 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 intrapartum or within 24 hours of delivery (27.7%), a third within 42 days of delivery (35.6%) and a minority 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 paper 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 CRADLE intervention into routine maternity care in ten regions across Zimbabwe, Zambia, Sierra Leone, Malawi, Ethiopia, Uganda, Haiti and India over 20 months from 1st April 2016 to 30th November 2017 (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 shock index displaying 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 to 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 3.3km to 74km to the referral centre. Community health care providers were included where they were formally involved in routine maternity care provision and supported at the district level.[7] The intervention was delivered to all health care professionals (HCP) working in gynaecology and maternity in the region facilities.

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 due to 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 01/04/2016 and 31/11/2017 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 were 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 health care professionals 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 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 finding) to ensure data completeness and all

outcomes checked to avoid double counting. Systematic reporting of community cases, for example through household surveys, were not undertaken. Therefore, community cases are included where reported and in these predominantly urban settings we consider most community deaths were made known to our researchers. All data was entered onto a standardized 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 due to the lack of existing process). This and all local ethical approvals were in place prior to the study start. Institutional-level consent on behalf of the cluster was obtained. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Funding

The CRADLE Trial was funded by the Medical Research Council, Department of Biotechnology India and Department of International Development joint fund (MR/N006240/1). This included external peer review. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Statistical methods and analysis

Statistical analyses were undertaken in Stata version 13.1. 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 association between ICU bed availability (average per 10,000 deliveries), blood transfusion availability (mean % of facilities) and health care professionals (average per 1000 deliveries) and maternal death by region used linear regression with 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 collected only 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 (range 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), the latter causes all with individual contributions less than 4%. The causes of death categorized 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: 15.2% in India to 44.5% in Uganda Centre 1; sepsis: 0.0% in Haiti to 27.5% in Zimbabwe, hypertensive disorders of pregnancy: 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 we could not rule out an effect (Table 2).

Half of pregnancy-related deaths (50.6%; n=505) occurred in women aged 20-29, 10.3% (n=103) in women aged under 20 years, 34.5% (n=344) in women aged 30-39 and 4.6% (n=46) in women aged ≥40. 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 those that occurred after delivery, the majority were within the first seven days after delivery (24.8%, n=248), with a further 11.1% (n=111) more than seven days after delivery (Figure 2 and Table S2). Across all the study regions, only 1.8% (n=18) 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 (range 38.3.0% 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).

Overall, the number of HCP 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 HCP available and the rates of pregnancy-related death in each region (OR 1.00; 1.00-1.01). Two regions, Sierra Leone and Uganda Centre 2, did not have any ICU facility 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; 0.18-2.63; 1 to 5 beds/1000 deliveries OR 132 (0.49-3.69), 6-10 beds per 1000 deliveries OR 0.65; 0.34-1.23). On average, blood transfusion was available in 25.1% of facilities (range 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 by 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 health care facilities (98.1%), after delivery (35.9%) and in women aged 20-29 (50.6%). Overall, the implementation of the CRADLE intervention was not associated with any significant change in rates of pregnancy-related death but the effect varied in individual sites. We did not identify any significant association between availability of key obstetric resources measured 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 inclusion of multiple settings. Existing prospective datasets are frequently small and measured at hospital level with limited information on 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 from primary health-care facilities and community cases.

The data were collected during a randomised controlled trial and therefore include measurement before and after 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 due to underreporting of community cases, since 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 to the literature.[4]

Due to 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, due to complex and late presentations to hospital and poor documentation. However, we have demonstrated that collection of maternal mortality data and entry onto a standardized electronic database is feasible across ten sites with varying infrastructure. It is a strength that this paper reports resource availability, but daily fluctuations in resource availability remains unknown. The number of HCPs working in maternity was higher than anticipated.[14] This may be due to the inclusion of untrained support staff or employed staff not regularly working and therefore 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.[16] Yet in this study, more than 20-fold variation in mortality was observed between regions suggesting 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 to 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 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 World Health Organisation (WHO).[12] Even physician-certified death may be complex due to limited diagnostic services and late presentation at the facility. Ongoing training and development of local policy in registering maternal deaths is required to ensure accuracy and comparability of 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, likely 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 indicates 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.[17] Evidence from low-income countries suggests that increasing facility delivery rate does not necessarily equate to improved maternal or neonatal outcomes due to poor quality of care, estimated to contribute to half of all maternal deaths.[18] Policy makers 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 from obstetric haemorrhage (36.0%). The WHO makes 32 evidence-based recommendations for prevention and treatment of post-partum haemorrhage.[19] Therefore, health care professionals and policy makers have the opportunity to target interventions to this high-risk period, focusing on access and timely delivery of proven, effective interventions.

In this study, the majority of deaths occurred in women aged 20-29, likely reflecting the greatest proportion of births occurring in this group, as opposed to 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 LMICs had undergone caesarean section (23.8%, 95% CI 21.0–26.7),[20] possibly reflecting the urban setting of our study. The elevated proportion of caesarean sections in this group is likely due to severe morbidity necessitating rapid delivery of the baby; however, it may also add to the literature that mortality risk is disproportionately high following caesarean section in LMICs.[20] This will likely be of increasing future importance as rates of caesarean delivery globally increase.[21] HCPs and policy makers need to address access to surgery and navigate the challenging balance of under and overuse,[22] 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 from haemorrhage, sepsis and pregnancy-associated hypertension. Given 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. However, interpretation is challenging as individual sites may be influenced by changes in mortality rates over time, irrespective of introduction of the intervention 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 dataset across eight low and middle-resource settings. These data highlight that mortality (for the woman and baby) remains high with pregnancy and the perinatal period needing ongoing prioritisation in research and policy. The high proportion of mortality in facility settings indicates that 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 evaluation to define the components that need focus to reduce mortality.

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Disclosure of interests

The authors have no conflict of interests to declare. The trial was funded by a government grant as outlined below. Completed disclosure of interest forms are available to view online as supporting information.

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Contribution to authorship

NV, PTS, LC and AHS designed this study, NV, EH, MFG, SG, SC, LYK, AB, UC, MB, AN, BV contributed to the acquisition of data and NV, PTS, JS, LC, AHS contributed to analysis and interpretation of the data. All authors were responsible for drafting the article and developing intellectual content.

Details of Ethics Approval

- **United Kingdom:** Biomedical Sciences, Dentistry, Medicine and Natural and Mathematical Sciences Research Ethics Subcommittee at King's College London; LRS-14/15-1484
- **Ethiopia:** Ethiopian Public Health Institute, Ethiopia; EPHI6.4/185
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- **Sierra Leone:** Office of the Sierra Leone Ethics and Scientific Review Committee Directorate of Training and Research, Connaught Hospital; Sierra Leone
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- **India:** K.L.E Society's Jawaharlal Nehru Medical College, Belgaum, India; MDC/IECHSR/2015-16/A-59; KLEU/EC/2016-17/A-95; KLEU/EC/2017-18-A-104

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- **Malawi:** National Health Sciences Research Committee at Zomba Central Hospital, Malawi; NHSRC 15/11/1504
- **Uganda:** Uganda National Council for Science and Technology; Uganda; HS1953

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Table 1: Maternal Death per 10,000 deliveries by region and by intervention

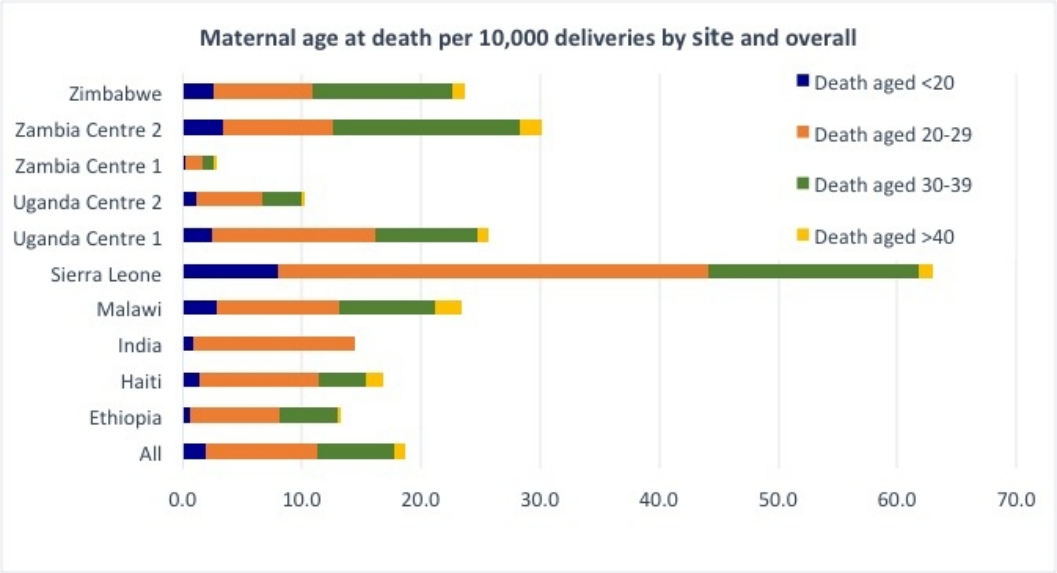
Region		Overall	Pre-intervention	Post-intervention
Ethiopia	Rate per 10,000 deliveries	13.3	13.1	13.6
	(n/N)	47/35429	32/24390	15/11039
Haiti	Rate per 10,000 deliveries	16.8	7.82	26.2
	(n/N)	25/14910	6/7670	19/7240
Sierra Leone	Rate per 10,000 deliveries	63.0	142	55.3
	(n/N)	150/23806	30/2106	120/21700
India	Rate per 10,000 deliveries	14.4	14.7	14.1
	(n/N)	33/22876	17/11531	16/11345
Malawi	Rate per 10,000 deliveries	23.5	24.3	20.8
	(n/N)	146/62165	117/48243	29/13922
Uganda Centre 1	Rate per 10,000 deliveries	25.7	28.9	24.9
	(n/N)	328/127817	72/24886	256/102931
Uganda Centre 2	Rate per 10,000 deliveries	10.2	9.7	11.1
	(n/N)	62/60502	36/37003	26/23499
Zambia Centre 1	Rate per 10,000 deliveries	2.8	6.4	0.5
	(n/N)	35/123476	31/48252	4/75224
Zambia Centre 2	Rate per 10,000 deliveries	30.1	27.6	31.3
	(n/N)	81/26869	23/8343	58/18526
Zimbabwe	Rate per 10,000 deliveries	23.7	25	11.2
	(n/N)	91/38383	87/34814	4/3569
All regions	Rate per 10,000 deliveries	**18.6**	**18.2**	**18.9**
	(n/N)	**998/536233**	**451/247238**	**547/288995**

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[Ω]	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** **998/536233**	**18.2** **451/247238**	**18.9** **547/288995**	**OR 0.79** **(0.30-2.09)**

*Analysis did not converge

[Ω]Eclampsia, pre-eclampsia or stroke



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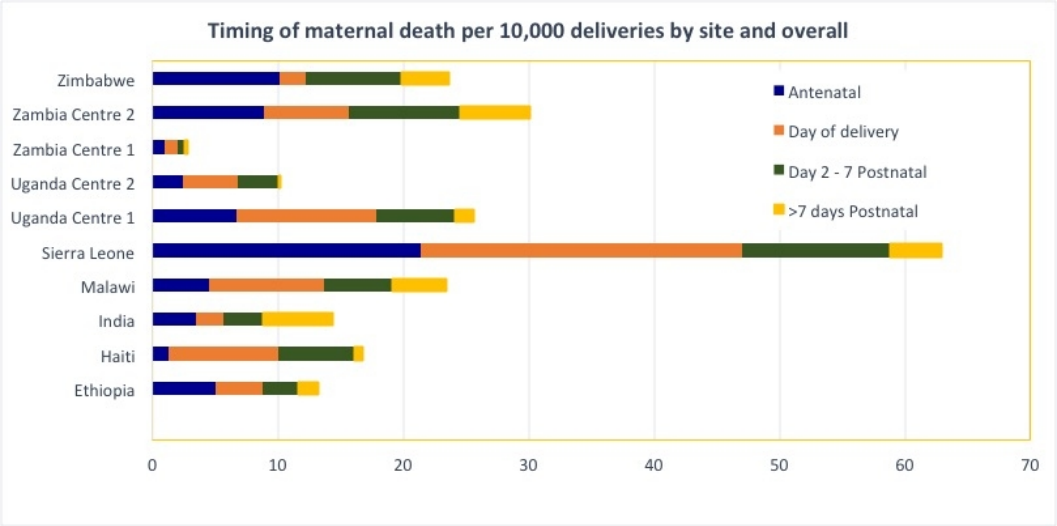

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