Global causes of maternal death

Say, Lale; Chou, Doris; Gemmill, Alison; Tunçalp, Özge; Moller, Ann-Beth; Daniels, Jane; Gülmezoglu, A Metin; Temmerman, Marleen; Alkema, Leontine

DOI:
10.1016/S2214-109X(14)70227-X

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Say, L, Chou, D, Gemmill, A, Tunçalp, Ö, Moller, A-B, Daniels, J, Gülmezoglu, AM, Temmerman, M & Alkema, L 2014, 'Global causes of maternal death: a WHO systematic analysis', *Lancet Global Health*, vol. 2, no. 6, pp. e323-333. https://doi.org/10.1016/S2214-109X(14)70227-X

Global causes of maternal death: a WHO systematic analysis

Lale Say, Doris Chou, Alison Gemmill, Özge Tunçalp, Ann-Beth Moller, Jane Daniels, A Metin Gülmezoglu, Marleen Temmerman, Leontine Alkema

Summary

Background Data for the causes of maternal deaths are needed to inform policies to improve maternal health. We developed and analysed global, regional, and subregional estimates of the causes of maternal death during 2003–09, with a novel method, updating the previous WHO systematic review.

Methods We searched specialised and general bibliographic databases for articles published between between Jan 1, 2003, and Dec 31, 2012, for research data, with no language restrictions, and the WHO mortality database for vital registration data. On the basis of prespecified inclusion criteria, we analysed causes of maternal death from datasets. We aggregated country level estimates to report estimates of causes of death by Millennium Development Goal regions and worldwide, for main and subcauses of death categories with a Bayesian hierarchical model.

Findings We identified 23 eligible studies (published 2003–12). We included 417 datasets from 115 countries comprising 60 799 deaths in the analysis. About 73% (1 771 000 of 2 443 000) of all maternal deaths between 2003 and 2009 were due to direct obstetric causes and deaths due to indirect causes accounted for 27·5% (672 000, 95% UI 19·7–37·5) of all deaths. Haemorrhage accounted for 27·1% (661 000, 19·9–36·2), hypertensive disorders 14·0% (343 000, 11·1–17·4), and sepsis 10·7% (261 000, 5·9–18·6) of maternal deaths. The rest of deaths were due to abortion (7·9% [193 000], 4·7–13·2), embolism (3·2% [78 000], 1·8–5·5), and all other direct causes of death (9·6% [235 000], 6·5–14·3). Regional estimates varied substantially.

Interpretation Between 2003 and 2009, haemorrhage, hypertensive disorders, and sepsis were responsible for more than half of maternal deaths worldwide. More than a quarter of deaths were attributable to indirect causes. These analyses should inform the prioritisation of health policies, programmes, and funding to reduce maternal deaths at regional and global levels. Further efforts are needed to improve the availability and quality of data related to maternal mortality.

Funding USAID, the US Fund for UNICEF through a grant from the Bill & Melinda Gates Foundation to CHERG, and The UNDP/UNFPA/UNICEF/WHO/The World Bank Special Programme of Research, Development, and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research.

Lancet Glob Health 2014; 2: e323–33

Published Online May 6, 2014 http://dx.doi.org/10.1016/S2214-109X(14)70227-X

See Comments page e302

UNDP/UNFPA/UNICEF/WHO/The World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland (L Say MD, D Chou MD, A Gemmill MPH, Ö Tunçalp MD, A-B Moller MSc, A M Gülmezoglu MD, M Temmerman MD); **Department of Demography, University of California, Berkeley, CA, USA** (A Gemmill); **Clinical Trials Unit, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK** (J Daniels PhD); **and Department of Statistics and Applied Probability and Saw Swee Hock School of Public Health, National University of Singapore, Singapore** (L Alkema PhD)

Correspondence to: Dr Lale Say, UNDP/UNFPA/UNICEF/WHO/The World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland **sayl@who.int**

Introduction

An estimated 287 000 maternal deaths occured worldwide in 2010, most of which were in low-income and middle-income countries and were avoidable.[1] Reduction of maternal mortality has long been a global health priority and is a target in the UN Millennium Development Goals (MDG) framework[2] and a key concern of the Global Strategy for Women's and Children's Health launched by the UN Secretary-General in September, 2010.[3] To reach the target of the fifth MDG, a 75% decrease in maternal mortality ratio (the number of maternal deaths per 100 000 livebirths) between 1990 and 2015 is needed. Some progress towards this target has been reported, especially in the past decade,[1,4–6] but further improvements are needed.

A key requirement for further advances in reduction of maternal deaths is to understand the causes of deaths for effective policy and health programme decisions. The definition of maternal mortality ("the death of a woman whilst pregnant or within 42 days of delivery or termination of pregnancy, from any cause related to, or aggravated by pregnancy or its management, but excluding deaths from incidental or accidental causes"[7]) allows the identification of maternal deaths on the basis of their causes, as either direct or indirect. However, collection of routine and complete information about causes of maternal death has not been possible because of inadequacies of data collection and absence of vital registration systems in most countries. The first systematic analysis of all available published scientific literature and government reports on causes of maternal death was published in 2006, and provided an overall picture of the contribution of different causes to the burden of maternal deaths. In 2006, we reported haemorrhage and hypertensive disorders as the leading causes of maternal mortality in developing regions.[8] More recently, the Global Burden of Disease (GBD) study[9] provided estimates of maternal causes of

death for the main direct causes as part of the analysis of all causes of death.

See Online for appendix

We analysed global, regional, and subregional estimates of the causes of maternal death during 2003–09, with a novel method. This period was chosen to avoid overlap with the previous review that covered 1998–2002.[8] The study period did not include reported deaths from more recent years to ensure increased comparability across countries; more recent data were not available for most countries, especially within the WHO mortality database that includes vital registration datasets made available by the countries. We also elaborated for the first time further breakdown of main cause of death categories, and provided cause of death estimates for disorders that are clinically important—eg, antepartum and postpartum haemorrhage.

Methods

Search strategy and selection criteria

We used the International Classification of Diseases (ICD, 10th edition) definition of maternal mortality,[7] and included maternal deaths reported during 2003–09, and generated regional estimates for the ten MDG regions.[10] We searched for data for causes of maternal death from two distinct sources. We used vital registration datasets from the WHO mortality database, made available by countries.[11] We deemed vital registration data as good quality if the completeness of death registration in the population older than 5 years was more than 85% and the proportion of ill-defined causes of death (coded as R99) were less than 20%. Details of how we assessed completeness and coverage of vital registration data by WHO mortality statistics are described elsewhere.[1]

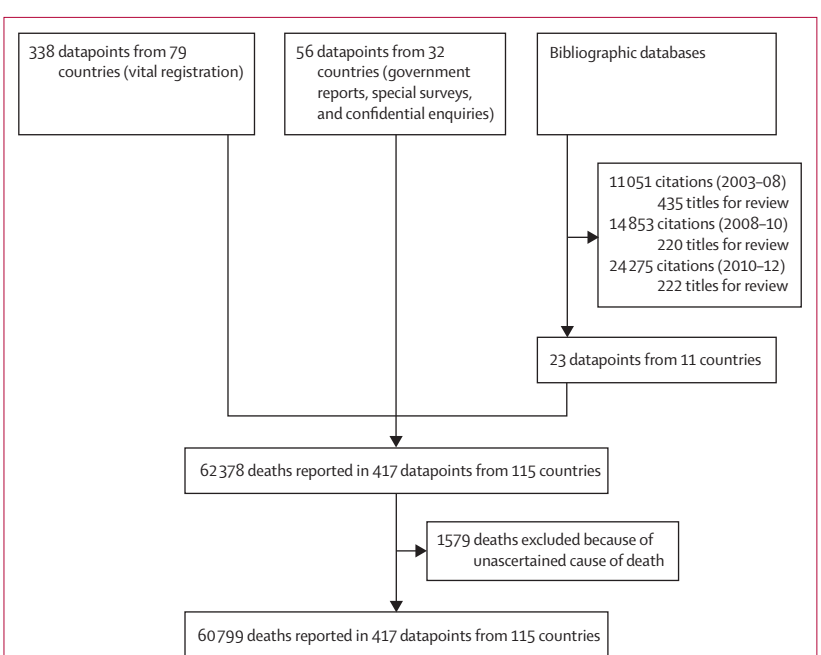

Figure 1: **Study profile**

We also did a literature search of bibliographic databases by adapting a previously described search strategy[12] (appendix). Two reviewers (ABM and DC) initially screened the citations identified by the searches on the basis of their titles and abstracts. The full text of the article was obtained if both reviewers judged a citation as potentially eligible and a third reviewer (JPD) adjudicated on discrepant opinions. A second round of screening of the full reports was done in the same way. Additionally, we identified government reports including cause-of-death information by hand searching WHO regional databases, websites of Ministries of Health and National Statistical Offices, and archives of relevant reports received by WHO. We considered studies identified through the literature search and governmental reports for inclusion if they reported data for the causes of maternal mortality between Jan 1, 2003, and Dec 31, 2009. We excluded studies that contained data before 2003 that could not be disaggregated from after 2002 data and with midpoint of the data collection period before 2003. In line with the 2006 review, we also excluded studies reporting fewer than 25 deaths or fewer than four major categories of death.[8] Lastly, we excluded studies in which more than 25% of deaths did not have a cause assigned. We considered subnational studies for inclusion only if investigators explicitly reported methods and if the maternal deaths that they reported were deemed to be representative of the population they pertained to. We included studies from health facilities or institutions only if the institutional birth rate was greater than or equal to 50% in that setting during 2003–09. The institutional birth rate was based on the national country reported figure derived from sources such as Demographic and Health Surveys, Multiple Indicator Cluster Surveys, and national health statistical reports.

If different data sources overlapped for a country period, we included only one data source, and national data took precedence over data from subnational levels in the following order: national enquiries, vital registration, and nationally representative surveys of maternal deaths. Thus, although countries might have had only one source of data for any particular year, more than one source might have been included in the entire study period 2003–09.

Data extraction and classification of maternal deaths

Data extraction from studies and reports was done by one reviewer (ABM) and independently checked on the form by another (JPD or DC). ICD-10 codes were used to classify causes of maternal death (appendix). Data using ICD-9 codes were converted to ICD-10 codes with the WHO ICD-10 Translator.[13] We excluded vital registration data from Russia, Kazakhstan, Belarus, and Ukraine reported with ICD 10-1 because accurate assignment of deaths to the equivalent ICD-10 codes or analytical pregnancy or obstetric categories was not possible. We assigned

research study data equivalent ICD-10 codes by matching the closest diagnosis. When data presented were ambiguous, contradictory, or could not be disaggregated, we tried to contact the author for clarification. If this was not successful, we used the consensus view of two of the authors (JPD, DC). Maternal deaths assigned to unknown as a cause of death were excluded from the analysis.

For analysis purposes, we grouped maternal causes of death into seven main categories of direct and indirect causes: abortion, embolism, obstetric haemorrhage, hypertensive disorders, pregnancy-related sepsis, other direct causes, and indirect causes. The abortion category includes induced abortion, miscarriage, and ectopic pregnancy. We defined the category of indirect maternal deaths in line with the WHO application of ICD-10 (ICD-MM) to deaths during pregnancy, childbirth, and the puerperium.[14] ICD-MM was published to enable a standardised grouping of causes of death and to avoid presentation of highly aggregated data in differing classification groups, complicating the task of data comparability. The broad ICD-MM categories were further subdivided. The category haemorrhage was divided into subcategories of antenatal, intrapartum, and postpartum haemorrhage; other direct causes were subcategorised into complications of delivery, obstructed labour, and all other direct causes. Indirect causes of death were subcategorised into medical disorders, HIV-related maternal deaths, and all other indirect causes.

Statistical analysis

For every country, we estimated the causes of death distribution on the basis of country-specific data (if available) and the regional causes of death distribution with a Bayesian hierarchical model. We estimated all causes and subcauses hierarchically except for the proportion of HIV/AIDS indirect deaths, which we modelled separately because of the dependence of the proportion on the severity of the HIV/AIDS epidemic in the country.

To construct country-specific HIV/AIDS-removed causes of death distribution, we divided countries into three categories on the basis of data availability and data quality. We divided countries with recorded causes of death distribution into categories A and B, and combined countries without any data in group C.[15] Category A included all countries with good quality and complete vital registration data, where the sample of maternal deaths (for which the recorded causes of death distribution was obtained) was deemed to be representative of the total number of maternal deaths for the country during the period of interest. For countries in category B for which vital registration data might have been available but not considered good quality, we assumed that the estimated causes of death distribution from the recorded samples were not necessarily representative of the causes of death distribution of all maternal deaths in the period of interest (appendix p 7).

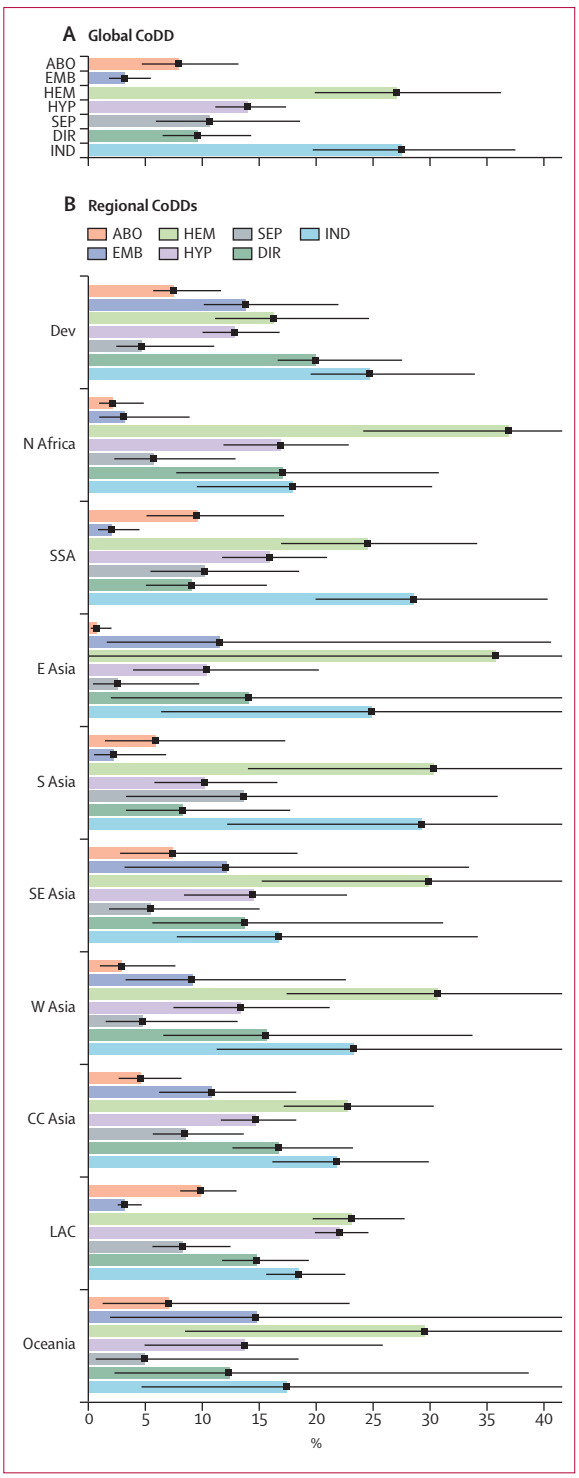

Figure 2: **Estimates for main causes of death worldwide**
Point estimates are shown by bars (and squares) and 95% uncertainty intervals are shown by the horizontal lines. CoDD=cause of death distribution. ABO=abortion. EMB=embolism. HEM=haemorrhage. HYP=hypertension. SEP=sepsis. DIR=direct causes. IND=indirect causes. Dev=developed regions. N Africa=northern Africa. SSA=sub-Saharan Africa. E Asia=eastern Asia. S Asia=southern Asia. SE Asia=southeastern Asia. W Asia=western Asia. CC Asia=Caucasus and central Asia. LAC=Latin America and the Caribbean.

We used the Bayesian hierarchical model for the HIV/AIDS-removed cause of death distribution to exchange information about these distributions between countries. With this method, the estimates in countries with scarce information were informed by the typical experience in the region, which is the HIV/AIDS-removed causes of death distribution that is unweighted by the country-specific total maternal deaths envelopes in the region. Additionally, in the hierarchical model, typical regional patterns in groups with scarce information were informed by patterns in other regions. For countries in group C, the cause of death distribution estimates were given by the typical regional estimates, and we assessed uncertainty on the basis of the estimated variability in, and correlation structure of, country-specific causes of death distribution within regions. For countries in group A with good quality vital registration data, the cause of death distribution was estimated from the recorded causes of death distribution, accounting for stochastic uncertainty—ie, uncertainty that arises when dealing with small numbers of observed deaths. For example, if only five deaths were recorded in a country, the underlying true cause of death distribution is uncertain. The extent of uncertainty in cause of death distribution for group A countries ranged from being negligible for countries where a large number of deaths were observed to substantial uncertainty for countries where causes of death for only a small number of deaths were recorded (eg, Belgium, where the causes of deaths for only five maternal deaths were recorded). For countries with substantial uncertainty on the basis of a small number of deaths, the hierarchical model informed the country-specific estimate, whereas for countries with less uncertainty, estimates were more data-driven and less informed by the hierarchical model. For countries in category B (where the recorded cause of death distributions were available for a subset of maternal deaths from vital registration or survey data), we assumed that the estimated causes of death distributions from the recorded samples were not necessarily representative of the causes of death distributions of all maternal deaths in the period of interest. For these countries, we assessed uncertainty in the cause of death distribution estimates for all maternal deaths without recorded causes on the basis of estimated variability in, and correlation structure of, country-specific cause of death distributions within regions. Therefore, the final estimated cause of death distributions for countries in group B accounted for stochastic uncertainty and additional uncertainty in the cause of death distributions for the unrecorded subset of maternal deaths.

The estimation of the proportion of HIV/AIDS maternal deaths was based on the approach used in the estimation of the total number of maternal deaths.[1,16] This approach provides country-specific estimates for the proportion of HIV/AIDS maternal deaths among all AIDS deaths to women of reproductive ages. These country-specific estimates were combined with estimates

	Abortion		Embolism		Haemorrhage		Hypertension		Sepsis		Other direct causes		Indirect causes	
	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)
Worldwide	193 000	7·9% (4·7–13·2)	78 000	3·2% (1·8–5·5)	661 000	27·1% (19·9–36·2)	343 000	14·0% (11·1–17·4)	261 000	10·7% (5·9–18·6)	235 000	9·6% (6·5–14·3)	672 000	27·5% (19·7–37·5)
Developed regions	1100	7·5% (5·7–11·6)	2000	13·8% (10·1–22·0)	2400	16·3 (11·1–24·6)	1900	12·9% (10·0–16·8)	690	4·7% (2·4–11·1)	2900	20·0% (16·6–27·5)	3600	24·7% (19·5–33·9)
Developing regions	192 000	7·9% (4·7–13·2)	76 000	3·1% (1·7–5·4)	659 000	27·1% (19·9–36·4)	341 000	14·0% (11·1–17·4)	260 000	10·7% (5·9–18·7)	232 000	9·6% (6·4–14·3)	668 000	27·5% (19·7–37·6)
Northern Africa	490	2·2% (0·9–4·9)	720	3·2% (0·9–8·9)	8300	36·9% (24·1–51·6)	3800	16·9% (11·9–22·9)	1300	5·8% (2·3–12·9)	3800	17·1% (7·7–30·8)	4000	18·0% (9·5–30·2)
Sub-Saharan Africa	125 000	9·6% (5·1–17·2)	27 000	2·1% (0·8–4·5)	321 000	24·5% (16·9–34·1)	209 000	16·0% (11·7–21)	134 000	10·3% (5·5–18·5)	119 000	9·0% (5·1–15·7)	375 000	28·6% (19·9–40·3)
Eastern Asia	420	0·8% (0·2–2·0)	6500	11·5% (1·6–40·6)	20 000	35·8% (10·9–68·2)	5900	10·4% (3·9–20·2)	1500	2·6% (0·4–9·7)	8000	14·1% (2·0–51·3)	14 000	24·9% (6·4–58·8)
Southern Asia	47 000	5·9% (1·5–17·3)	17 000	2·2% (0·5–6·8)	238 000	30·3% (14·0–54·8)	80 000	10·3% (5·8–16·6)	107 000	13·7% (3·3–35·9)	65 000	8·3% (3·3–17·7)	229 000	29·3% (12·2–55·1)
Southeastern Asia	11 000	7·4% (2·8–18·4)	18 000	12·1% (3·2–33·4)	44 000	29·9% (15·2–51·3)	21 000	14·5% (8·4–22·7)	8100	5·5% (1·8–15·0)	20 000	13·8% (5·6–31·2)	25 000	16·8% (7·8–34·2)
Western Asia	860	3·0% (1·0–7·6)	2600	9·2% (3·3–22·6)	8900	30·7% (17·4–49·1)	3900	13·4% (7·5–21·2)	1400	4·8% (1·5–13·1)	4500	15·6% (6·6–33·7)	6700	23·4% (11·3–43·1)
Caucasus and central Asia	250	4·6% (2·7–8·2)	590	10·9% (6·2–18·2)	1200	22·8% (17·2–30·3)	790	14·7% (11·6–18·3)	460	8·5% (5·7–13·6)	910	16·8% (12·6–23·2)	1200	21·8% (16·2–29·9)
Latin America and Caribbean	6900	9·9% (8·1–13·0)	2300	3·2% (2·6–4·7)	16 000	23·1% (19·7–27·8)	15 000	22·1% (19·9–24·6)	5800	8·3% (5·6–12·5)	10 000	14·8% (11·7–19·4)	13 000	18·5% (15·6–22·6)
Oceania	290	7·1% (1·2–22·9)	610	14·8% (1·9–47·6)	1200	29·5% (8·5–61·7)	560	13·8% (4·9–25·8)	200	5·0% (0·6–18·5)	510	12·4% (2·3–38·7)	710	17·4% (4·7–44·3)

Data shown are the estimated proportion of cause of death (%) with 95% uncertainty interval (95% UI).

Table 1: **Distribution of causes of deaths by Millennium Development Goal regions**

of the number of AIDS, maternal, and total deaths to women of reproductive ages to obtain an initial mean estimate for the proportion of HIV/AIDS maternal deaths. These estimates were updated with country-specific data on the proportion of HIV/AIDS deaths.

We used a Markov Chain Monte Carlo algorithm to generate samples of the posterior distributions of all model parameters, including the country-specific causes of death distributions. Point estimates for proportions were given by the posterior means of the proportion and 95% uncertainty intervals were given by the 2·5th and 97·5th percentiles of the posterior distributions. We calculated the resulting distribution for each region from the regional weighted averages of the estimated country-specific cause of death distributions in the region. Weights were based on the estimated number of maternal deaths for each country for the year 2005 (which is the estimation year closest to the midpoint of the study period).[1] The Markov Chain Monte Carlo sampling algorithm was implemented in R (version 3.0.1) and JAGS (version 3.3.0).[17,18]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 summarises the identification and selection of data for incorporation into the model. We included vital registration data from 79 countries, covering 338 country-year datapoints during 2003–09, of which 263 (78%) came from 58 countries with a good quality registration system. Of the 50179 citations identified from bibliographic databases, 23 studies from 11 countries met the inclusion criteria. Government reports, such as specialised statistical tabulations and surveillance documents, were available for a further 32 countries. These reports included "confidential enquiries", "RAMOS", or specialised "maternal mortality surveys". Four countries (France, UK, South Africa, and Mexico) produced confidential enquiries or reports of enhanced surveillance systems covering 12 country-years, which were judged better than vital registration data for that country. 26 datasets were informed by verbal autopsy; however, only ten of these datasets specified the verbal autopsy instrument used. The appendix shows further details of source of data by country and the studies providing the datasets.

All included data sources combined provided 417 datapoints from 115 countries and reported 62 378 deaths. Of these, we excluded 1579 deaths (2·5%), almost exclusively from studies and governmental reports, because no main cause of death could be ascertained (appendix). Of the 60799 maternal deaths included in the final database, 50% came from vital registration data, 29% from sub-Saharan Africa, and 2% from southern Asia. Considering the total estimated number of maternal deaths over 7 years, the study data represents 2.5% of all maternal deaths in that period.[4]

Figure 2 shows the regional and global estimates of distribution of causes of death. Nearly 73% of all maternal deaths between 2003 and 2009 were due to direct obstetric causes whereas deaths due to indirect causes accounted for 27·5% (95% UI 19·7–37·5) of all deaths from known causes (table 1). Haemorrhage was the leading direct cause of maternal death worldwide, representing 27·1% (19·9–36·2) of maternal deaths. More than two thirds of reported haemorrhage deaths were classified as postpartum haemorrhage (table 2). Hypertension was the second most common direct cause worldwide (14·0%, 11·1–17·4). Maternal mortality due to sepsis was 10·7% (5·9–18·6), abortion accounted for 7·9% (4·7–13·2), and embolism and other direct causes accounted for the remaining 12·8% of global deaths.

Table 3 shows the other direct causes of maternal mortality. Complications of delivery were responsible for 2·8% (1·6–4·9) and obstructed labour for 2·8% (1·4–5·5) of all maternal deaths worldwide, both reported within the other direct category, which accounted for 9·6% of all maternal deaths worldwide. Further breakdown of deaths due to indirect causes suggests that more than 70% of indirect causes are

	Antepartum		Intrapartum		Postpartum		Haemorrhage total	
	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)
Worldwide	158 000	6·5% (4·3–9·6)	23 000	0·9% (0·4–2·2)	480 000	19·7% (12·9–28·9)	661 000	27·1% (19·9–36·2)
Developed regions	700	4·8% (3·3–7·9)	510	3·5% (1·6–11·1)	1200	8·0% (4·7–15·5)	2400	16·3% (11·1–24·6)
Developing regions	157 000	6·5% (4·3–9·6)	23 000	0·9% (0·4–2·2)	479 000	19·7% (12·9–29)	659 000	27·1% (19·9–36·4)
Northern Africa	720	3·2% (1·5–6·2)	380	1·7% (0·3–6·8)	7200	32·0% (18·9–47·3)	8300	36·9% (24·1–51·6)
Sub-Saharan Africa	110 000	8·4% (5·0–13·7)	12 000	0·9% (0·2–3)	200 000	15·2% (8·6–25·1)	321 000	24·5% (16·9–34·1)
Eastern Asia	3800	6·6% (1·6–17·4)	210	0·4% (0·1–1·7)	16 000	28·7% (6·1–63·9)	20 000	35·8% (10·9–68·2)
Southern Asia	30 000	3·8% (1·5–8·5)	3400	0·4% (0·1–1·5)	205 000	26·1% (10·4–51·4)	238 000	30·3% (14·0–54·8)
Southeastern Asia	7000	4·7% (2·0–10·7)	3100	2·1% (0·3–8·7)	34 000	23·1% (9·4–46·1)	44 000	29·9% (15·2–51·3)
Western Asia	1700	6·0% (2·9–11·7)	710	2·5% (0·4–10·4)	6400	22·2% (10·1–41·5)	8900	30·7% (17·4–49·1)
Caucasus and central Asia	280	5·2% (3·5–7·9)	230	4·2% (1·6–10·7)	720	13·4% (9·4–19·8)	1200	22·8% (17·2–30·3)
Latin America and Caribbean	4000	5·8% (4·5–7·8)	2900	4·1% (2·1–9·0)	9200	13·3% (10·9–16·4)	16 000	23·1% (19·7–27·8)
Oceania	200	4·8% (1·0–13·8)	76	1·8% (0·1–11·3)	940	22·9% (4·1–57·8)	1200	29·5% (8·5–61·7)

Percentages shown are the subgroup as a proportion of all deaths for that region in the input dataset.

Table 2: **Subgroup analysis of haemorrhage deaths by Millennium Development Goal region**

from pre-existing disorders, including HIV, when exacerbated by pregnancy (table 4). HIV alone accounted for 5·5% (3·8–7·6) of global maternal deaths.

The global distribution was affected by the two regions, sub-Saharan Africa and southern Asia, that accounted for 83·8% of all maternal deaths. Although estimated regional cause of death distributions are quite uncertain for many causes, point estimates show substantial differences across regions (table 1 and figure 3). Haemorrhage accounted for 36·9% (24·1–51·6) of deaths in northern Africa, but only for 16·3% (11·1–24·6) in developed regions. Hypertensive disorders were a particularly important cause of death in Latin American and the Caribbean, contributing to 22·1% (19·9–24·6) of all maternal deaths in the region. Almost all sepsis deaths were recorded in the developing countries, and the proportion of such deaths was highest at 13·7% (3·3–35·9) in southern Asia.

Only a small proportion of deaths are estimated to result from abortion in eastern Asia (0·8%, 0·2–2·0), where access to abortion is generally less restricted. Latin America and the Caribbean, and sub-Saharan Africa have a higher proportion of deaths in this category than the global average; 9·9% (8·1–13·0) and 9·6% (5·1–17·2), respectively. Another direct cause, embolism, accounted for more deaths than its global average in southeastern Asia (12·1%, 3·2–33·4) and eastern Asia (11·5%, 1·6–40·6).

	Complications of delivery		Obstructed labour		Other		Other direct causes total	
	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)
Worldwide	68 000	2·8 (1·6–4·9)	69 000	2·8 (1·4–5·5)	98 000	4 (2·2–7·5)	235 000	9·6 (6·5–14·3)
Developed regions	760	5·2 (3·7–9·0)	94	0·6 (0·3–1·7)	2100	14·1 (11·8–20·9)	2900	20 (16·6–27·5)
Developing regions	67 000	2·8 (1·5–4·9)	69 000	2·9 (1·4–5·5)	96 000	3·9 (2·1–7·4)	232 000	9·6 (6·4–14·3)
Northern Africa	1600	7·3 (2·9–15·9)	210	0·9 (0·2–3·3)	2000	8·8 (2·6–20·9)	3800	17·1 (7·7–30·8)
Sub-Saharan Africa	43 000	3·3 (1·5–6·7)	28 000	2·1 (0·7–5·2)	48 000	3·7 (1·4–8·6)	119 000	9 (5·1–15·7)
Eastern Asia	250	0·4 (0·1–1·4)	6900	12·3 (0·9–50·1)	770	1·4 (0·2–5·8)	8000	14·1 (2–51·3)
Southern Asia	14 000	1·8 (0·4–5·2)	21 000	2·7 (0·5–8·5)	30 000	3·8 (0·9–10·3)	65 000	8·3 (3·3–17·7)
Southeastern Asia	3000	2·1 (0·5–6·6)	9400	6·4 (1·4–20·6)	7800	5·3 (1·3–17·3)	20 000	13·8 (5·6–31·2)
Western Asia	2000	7·1 (2·4–17·9)	320	1·1 (0·2–4·2)	2200	7·5 (2–23·2)	4500	15·6 (6·6–33·7)
Caucasus and central Asia	400	7·3 (5·2–10·9)	47	0·9 (0·4–1·9)	460	8·6 (5·6–14·4)	910	16·8 (12·6–23·2)
Latin America and Caribbean	2300	3·3 (2·6–4·9)	3300	4·8 (3·2–8·3)	4700	6·7 (4·8–10·3)	10 000	14·8 (11·7–19·4)
Oceania	95	2·3 (0·3–8·9)	210	5·1 (0·3–25·5)	210	5·1 (0·4–23·5)	510	12·4 (2·3–38·7)

Percentages shown are the subgroup as a proportion of all deaths for that region in the input dataset.

Table 3: **Subgroup analysis of other direct causes of death by Millennium Development Goal region**

The proportion of deaths due to indirect causes was highest in southern Asia (29·3%, 12·2–55·1), followed by sub-Saharan Africa (28·6%, 19·9–40·3). Indirect causes also accounted for nearly a quarter of deaths in the developed regions. The overall proportion of HIV maternal deaths is highest in sub-Saharan Africa, 6·4% (4·6–8·8%). The appendix shows estimates for country-specific cause of death distributions.

Discussion

This systematic analysis suggests that indirect causes and haemorrhage are the largest causes of maternal death worldwide. Of the direct causes of death, haemorrhage was the leading cause of maternal death, followed by hypertensive disorders and sepsis. Regional estimates varied substantially.

We scanned and included many data sources including government reports and peer-reviewed scientific literature (panel). Because of the paucity of data, all data for a country were aggregated during the 7-year period and model-based estimates were constructed for the large subset of countries without any information about their causes of death distributions. This approach differs from the previous WHO systematic review[8] in which recorded country-specific cause of death distributions were weighted by the number of maternal deaths in the country to obtain regional estimates. The new approach was implemented to overcome the drawback of the previous study that a recorded cause of death distribution based on a small sample size in a country with a large number of maternal deaths could unduly affect the regional estimates of the cause of death distribution. In the estimation method applied in this study, country-specific estimates of cause of death distribution were informed by the available data in the country and the regional average cause of death distribution, which can be regarded as a typical pattern for the region (unweighted by the total maternal death envelopes of the countries in the region) through a Bayesian hierarchical model. The accuracy of the regional and global estimates and 95% uncertainty intervals were validated through two out-of-sample validation exercises and suggested satisfactory model performance (appendix).

The different analytical approaches of the previous WHO review published in 2006 and the present analysis limit our ability to make comparisons between the findings of both. Furthermore, the limitations of the dataset and the methods used in the previous study did not allow for generation of a worldwide cause-of-death estimate, and only estimates for large world regions were calculated. However, some of the region-specific trends reported in the previous analysis also seem to be found in the present study. These include, for example, the highest share of haemorrhage deaths in Asian regions, the particular importance of hypertensive disorders of pregnancy in Latin America and the Caribbean, and the importance of indirect causes in sub-Saharan Africa.

Ultimately, the results of this analysis are constrained by the accuracy of the data included. Cause of death data are especially difficult to analyse because of inadvertent errors such as misclassification and misinterpretation of cause of death coding rules, or omissions or incorrect entries because of the nature of some of the disorders leading to maternal deaths such as abortion. We recognise the limitations due to the particular issue of misclassification within maternal death certification.

Although algorithms have been developed to adjust for misclassification of deaths in so-called garbage codes,[32] such algorithms are not able to improve on misclassification within maternal cause categories or the under-reporting of deaths of specific maternal causes. In view of the range of classification and under-reporting issues, and the limited information available to accurately adjust data, we opted to report aggregated cause of death fractions as reported in good vital registration or as predicted by the model based on unadjusted data. Therefore, resulting estimates should be interpreted as the estimates for the reported cause of death distribution.

An alternative estimation method was used more recently in the GBD Study 2010 to obtain estimates for the all-cause cause of death distribution, whereby a subset of misclassification issues were accounted for.[9,33] The GBD broad categorisation of causes of maternal death differed from our approach, with important differences for some categories. For example, the GBD did not use a category of indirect causes. Likewise, we included obstructed labour as a subcategory of other direct causes, in line with the ICD-MM, whereas the GBD study regarded it as a main category.[9] Inclusion of various disorders within identified categories also differed. For example, long labour is included in the obstructed labour category in our analysis, but not in the GBD study. Nevertheless, broad agreement exists between our global estimates and the GBD estimates (appendix).

However, estimates on maternal causes of death should be viewed with caution. Although future research on improved modelling approaches to deal with misclassification errors might lead to improved estimates, the absence of reliable data is a more pressing issue that demands increased prioritisation.

Recommendations for policy and practice

Our results show two main concerns for policy and practice related to data availability and quality in the countries. First, where data are most needed, data are often not available, which is unfortunately the case in some countries with high mortality where estimates were obtained on the basis of modelling. In this analysis, India and Nigeria together accounted for a third of global maternal deaths, but only one dataset met criteria for inclusion (India). Of the ten countries with the highest maternal mortality ratio in 2010, data were available only for one, Cameroon. Moreover, only 5% of all deaths included in the analysis were from southern Asia where the second highest number of maternal deaths were recorded. This means that cause of death distribution in a region is affected by the countries that have data within that region. Although the distribution is expected to be similar across countries within a region, for some conditions where availability of interventions significantly vary because of structural factors that are also highly contextual, such as the legal status of abortion, differences are expected.

Second, where data are available, they are often incomplete. For example, we noted that indirect deaths accounted for 27·5% (19·7–37·5) of deaths, although the actual indirect causes were not well delineated in more than a fifth of the reported indirect maternal deaths. Although it might be difficult to establish with certainty whether a woman's pregnancy aggravated a pre-existing medical disorder, or if their interaction resulted in her death, improved documentation on the sequence of events is paramount. For instance, differentiation between indirect maternal deaths due to HIV and direct maternal deaths in HIV-positive women is important; this difference would have implications at both clinical and programmatic levels. Accelerated action is needed to improve data acquisition and quality, especially relating to correct attribution of cause of death information.

	HIV-related		Pre-existing medical conditions		Other indirect causes		Indirect causes total	
	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)
Worldwide	134 000	5·5% (3·8–7·6)	361 000	14·8 (9·2–23·4)	177 000	7·2% (3·5–14·6)	672 000	27·5% (19·7–37·5)
Developed regions	400	2·7% (1·0–5·1)	3000	20·3 (16·1–29·1)	250	1·7% (0·9–4·4)	3600	24·7% (19·5–33·9)
Developing regions	133 000	5·5% (3·8–7·7)	358 000	14·8 (9·1–23·5)	177 000	7·3% (3·5–14·7)	668 000	27·5% (19·7–37·6)
Northern Africa	760	3·4% (1·1–6·4)	2800	12·4 (5·3–24·1)	500	2·2% (0·6–7·2)	4000	18·0% (9·5–30·2)
Sub-Saharan Africa	84 000	6·4% (4·6–8·8)	168 000	12·8 (7·0–22·3)	122 000	9·3% (4·6–18·4)	375 000	28·6% (19·9–40·3)
Eastern Asia	2200	3·9% (0·3–10·6)	12 000	20·7 (3·5–54·4)	130	0·2% (0·0–1·1)	14 000	24·9% (6·4–58·8)
Southern Asia	37 000	4·8% (1·2–10·2)	143 000	18·2 (6·1–41·9)	49 000	6·3% (0·5–25·3)	229 000	29·3% (12·2–55·1)
Southeastern Asia	5900	4·0% (1·4–8·3)	17 000	11·8 (4·1–28·7)	1400	1·0% (0·2–3·5)	25 000	16·8% (7·8–34·2)
Western Asia	1200	4·2% (1·5–8·4)	4900	16·9 (6·5–36·5)	650	2·2% (0·5–8·1)	6700	23·4% (11·3–43·1)
Caucasus and Central Asia	130	2·3% (1·0–4·1)	920	16·9 (11·9–24·7)	140	2·5% (1·4–5·1)	1200	21·8% (16·2–29·9)
Latin America and Caribbean	1300	1·8% (0·9–3·0)	9800	14·0 (11·7–17·6)	1800	2·6% (1·9–4·5)	13 000	18·5% (15·6–22·6)
Oceania	170	4·2% (0·5–11·1)	500	12·3% (1·9–38·2)	36	0·9% (0·1–4·4)	710	17·4% (4·7–44·3)

Percentages shown are the subgroup as a proportion of all deaths for that region in the input dataset.

Table 4: **Subgroup analysis of indirect causes of death by Millennium Development Goal region**

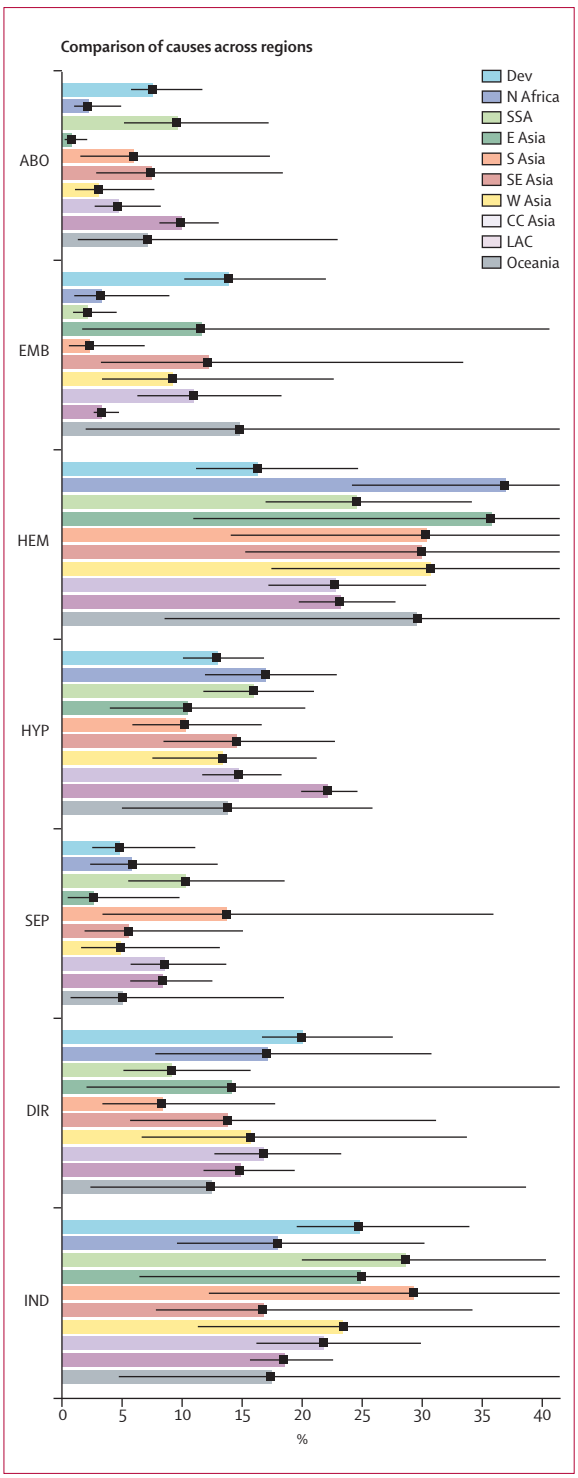

Figure 3: **Estimates for main causes of death by region**
Point estimates are shown by bars (and squares) and 95% uncertainty intervals are shown by the horizontal lines. ABO=abortion. EMB=embolism. HEM=haemorrhage. HYP=hypertension. SEP=sepsis. DIR=direct causes. IND=indirect causes. Dev=developed regions. N Africa=northern Africa. SSA=sub-Saharan Africa. E Asia=eastern Asia. S Asia=southern Asia. SE Asia=southeastern Asia. W Asia=western Asia. CC Asia=Caucasus and central Asia. LAC=Latin America and the Caribbean.

We included several sources of cause of death data, the quality of which depends on who completed the death certificate or verbal autopsy, who interpreted the information from the death certificate or verbal autopsy, and whether medical records were available for review to confirm or revise the ascertained cause of death. Confidential enquires and special maternal death reviews can provide such information, but the feasibility of doing such detailed reviews is very restricted.

To support data acquisition and quality needs, revisions are being made to the standard verbal autopsy instrument to increase the feasibility of its implementation where cause of death attribution is possible only by those means. Furthermore, the ICD-MM will standardise documentation and analysis related to maternal causes of death and their attribution to direct and indirect causes.[14] Discrepancies exist in how some deaths are categorised. For example, suicide in some contexts is regarded as coincidental whereas in other settings it might be reported within direct or indirect maternal deaths. Maternal suicides are known to happen in the context of undesired pregnancy, inability to access abortion, and postpartum depression or psychosis. ICD-MM suggests that maternal suicides will be included within the direct category of maternal death. With the process for the 11th revision of the ICD well underway,[34] one can anticipate the possibility for improved granularity of data. But one must also recognise the responsibility of the certifying professional to provide accurate and useful information for improved epidemiological monitoring and assessment to inform policies with the best available evidence. Calls for inclusion of training on cause of death certification and the use of ICD use within medical curricula are well founded and should be supported. Still, these calls for better data need to acknowledge the realities in establishing, with accuracy, what the cause of death was at time of certification. This need for accuracy is especially important in relation to identification of indirect maternal deaths that aim to establish the aggravating effect between the physiological effects of pregnancy and another disease.

With regard to clinical implications, we find that, despite established interventions to prevent and treat postpartum haemorrhage (eg, active management of the third stage of labour[35]), haemorrhage remains the leading individual cause of death. With available data, it is not possible to establish whether the persistence of haemorrhage as the leading cause of death despite effective interventions is the result of a failure to implement such interventions, whether there is a shift towards antepartum haemorrhage or a shift in delivery practice such as increasing rates of caesarean sections, or whether misclassifications with regard to abortion and obstructed labour are erroneously increasing the haemorrhage category.

Further analysis to elucidate the separate contribution of antepartum and postpartum causes will have important implications for the planning and implementation of policy

Panel: Misclassification and underreporting issues by cause of death

Abortion

We estimated that 7·9% (95% UI 4·7–13·2) of all maternal deaths were due to abortion. This finding is lower than the previous assessments, which estimated mortality due to unsafe abortion at 13%.[19,20] Classification of maternal deaths due to abortion, and more specifically unsafe abortion, is associated with a risk of misclassification, which might lead to underreporting. Even where induced abortion is legal, religious and cultural perceptions in many countries mean that women do not disclose abortion attempts and relatives or health-care professionals do not report deaths as such. Under-registration of deaths might be the result of stigmatisation of abortion affecting what information is reported by relatives and informants or intentional misclassification by providers when abortion is restricted.[21]

In these circumstances, the overall number of maternal mortality might not be affected, whereas abortion-related deaths might be particularly underestimated because of this under-reporting. Although these abortion-related deaths might be classified mainly into sepsis and haemorrhage, this might over-simplify the complexity of death reporting. An analysis[22] comparing International Classification of Diseases 10 (ICD-10) codes for underlying cause of death with the remainder of information about the death certificate and verbal autopsy in rural Mexico found that deaths due to second trimester abortion were misclassified into both maternal and non-maternal deaths. Examples of misclassification included assigning underlying cause of death from amniotic fluid embolism to cerebral anoxia, rather than abortion, either induced or spontaneous. Validation studies like this provide needed insight into the quality and accuracy of maternal mortality data. However, short of reviewing every death certificate and medical record after the death of a woman aged 15–49 years, the study further highlights the difficulty associated with considering adjustments to account for this type of misclassification, or indeed any misclassification. Validation studies can identify patterns of systematic or unbalanced misclassification, but the validity of application of adjustment parameters derived by verbal autopsy data from one location to another, and application of factors from hospital-based studies to population-based data, can be problematic.[23]

Obstructed labour

Deaths that happen after obstructed labour and its consequences are hard to measure because they can be coded as uterine rupture, haemorrhage, or sepsis. This is especially problematic in settings where verbal autopsies are used to establish cause of death. Verbal autopsy methods do not have consistent case definitions, which creates confusion regarding hierarchical assignment of causes and subsequently affects the validity of the study data.[24] A specific mention is warranted to clarify the classification of obstructed labour in this study, which is subsumed into direct causes of death, following guidance from ICD-MM.[14] Although from a clinical perspective, obstructed labour is commonly understood as a phenomenon by which a woman might die in labour, from an epidemiological and classification standpoint, it is inappropriate to identify obstructed labour as a cause of death.

The ICD-10 aims to capture the initiating step most relevant to public health in the sequence leading to death, because preventing this disorder would prevent not just the death, but all of the illness, complications, and disability that preceded it. In these cases of obstructed labour, death might be prevented by access to operative delivery. However, when the only available information from a lay reporter suggests that the woman seemed to be in labour, or in pain, for a long time before death, little is actually known about the sequence of events that leads to death, or about the progress of labour. These deaths might be misattributed to obstructed labour, leading to overestimation of the proportion that could be prevented through operative delivery and underestimation of the need for other services. In most settings, the implementation of ICD-10 coding does not allow dual coding for cause of death—eg, obstructed labour and sepsis, or obstructed labour with uterine rupture and haemorrhage. Proposals for the ICD-11 revision link the disorders, thereby satisfying the need for clinicians to document obstructed labour while ascertaining the cause of death.

Indirect causes of death (excluding HIV/AIDS)

The phenomenon of misattribution of indirect maternal causes of death, resulting in underestimation of 20–90% of maternal deaths, has been described in a number of settings.[25–30] In Austria, misclassification was significantly higher for indirect deaths (81%, 95% CI 64–91) than direct deaths (28%, 21–36),[31] whereas in the UK, indirect deaths accounted for up to 74% of under-reported maternal deaths during 2003–05.[30]

HIV/AIDS

Under-reporting and misclassification of indirect maternal deaths due to HIV/AIDS are especially problematic. Although verbal autopsy might be able to measure AIDS mortality,[43] hospital data-based validation studies might not be useful in adjusting for the effect of misclassification error in the estimates of cause-specific mortality fractions at the population level.[23]

When deaths happen in a facility, death certificate reporting might show only HIV as a cause of death and not an obstetric complication such as sepsis. This situation highlights the need for specific review of deaths of women infected with HIV temporal to pregnancy. The woman might die from HIV or with HIV while pregnant. Since 2010, this distinction is now possible from the standpoint of statistical tabulation as per ICD-10 coding. Our analyses precede the changes in ICD-10 coding and so a decision was made to consider cases where HIV was listed as a cause of maternal death, whether by description or use of a B code, as an indirect maternal death. As these data are scarce, the proportion of indirect maternal deaths due to HIV is probably underestimated in this study. It is anticipated that as methods for global maternal death estimation evolve, evidence of the parameters needed to estimate indirect maternal HIV deaths and further clarification on the use of ICD-10 codes will standardise and improve our understanding of maternal and HIV death tallies.[14]

and programmes, because interventions to address them are very different. Although the international community has rightly focused on postpartum haemorrhage, and specifically atonic postpartum haemorrhage, it is now the appropriate time to unpack the obstetric haemorrhage category. The improved method used in this analysis allowed delineation of haemorrhage deaths, reporting that about 24·0% of all haemorrhage deaths happened during pregnancy, and the remainder in the intrapartum or postpartum period. Thus we provide for the first time an evidence-based estimation of the proportion of maternal deaths due to antepartum haemorrhage.

Also alarming is the proportion of deaths attributed to hypertensive disorders, which are the second highest

worldwide among all direct causes and the most prominent cause in the Latin America and Caribbean region. This finding is despite the well established evidence that magnesium sulphate more than halves the risk of death from pre-eclampsia.[36–39] Although magnesium sulphate is deemed an essential drug by WHO,[40] the problem is the extent to which it is available and appropriately used in most countries. A systematic review on the prevalence of pre-eclampsia and eclampsia described the barriers to the use of magnesium sulphate as drug licensing and availability, inadequate and poorly implemented clinical guidelines, and insufficient political support for policy change.[41] More recently, a WHO survey[42] of delivery care in more than 300 health facilities in 29 countries highlighted that, even if coverage of magnesium sulphate is high in cases where coverage is needed, the overall mortality due to eclampsia was not reduced, highlighting the fact that more attention to other elements of quality of care is also needed.

The large proportion of deaths attributed to indirect causes cannot be ignored. As direct maternal deaths decrease because of targeted interventions, efforts to reduce maternal mortality will have to be refocused on reduction of indirect causes. Although emphasis has been placed on linking maternal and HIV care, addressing the needs of women with pre-existing comorbid disorders such as cardiac and endocrine disease in pregnancy will need additional links between obstetric and other medical specialties. This situation is further complicated as the burden of non-communicable diseases is high in developing countries where health systems are poorly equipped to coordinate specialised care. The four main non-communicable diseases are cardiovascular diseases, cancers, diabetes, and chronic respiratory diseases.[43] Among these diseases, diabetes, cardiovascular, respiratory disorders, and cancers are of particular concern among reproductive aged women for their potential contribution as indirect causes for both morbidity and mortality. Further focus on understanding the true burden of these disorders in pregnancy, and on the changing demographics of disease patterns, is warranted.

The gaps in coverage of effective interventions, for both direct and indirect causes of deaths, according to their distribution in various settings have large implications in view of the urgent need to accelerate the rate of decrease in maternal mortality to reach the MDG5 target and further to end all preventable maternal deaths.[44] Therefore, accurate and routine information about causes of maternal deaths is crucial in both implementation of interventions and tracking and interpretation of the gaps in coverage.

Contributors

LS and AMG conceived the review. All authors developed the methods. A-BM did the literature search and prepared the vital registration data. AB-M, DC, and JPD considered studies for inclusion and extracted the data. LA developed the statistical model and did the statistical analysis. All authors provided input to the interpretation of the results. LS, OT, DC, and LA prepared the manuscript and supplementary material. All authors provided input to the manuscript and approved the final version.

Declaration of interests

Five WHO staff members (LS, DC, ÖT, AMG, and MT) are part of the team that did the study. The findings in this paper represent the conclusions of the authors. We declare that we have no further competing interests.

Acknowledgments

We thank Andrew Howman and Rita Champaneria for their assistance with the literature searching and data management; the Child Health Epidemiology Reference Group (CHERG) for their technical review; Cristina Cuesta, Gilda Piaggio, Zoe Matthews, and Colin Mathers for their advice on the statistical methods; and Alexandra Furmston, Lixia Dou, Naomi Lee, Celia Liu, João Paulo Dias De Souza, Roderik F Viergever, Karmela Krleža-Jerić Irena Zakarija-Grkovic, and the Croatian Branch of the Italian Cochrane Centre for their assistance with translating reports for this study.

References

1 WHO, UNICEF, UNFPA, The World Bank. Trends in maternal mortality: 1990 to 2010. WHO, UNICEF, UNFPA, and The World Bank Estimates, 2012.
2 United Nations. United Nations Millennium Development Goals. 2013. http://www.un.org/millenniumgoals/maternal.shtml (accessed Feb 28, 2014).
3 United Nations' Secretary General. Global Strategy for Women's and Children's Health. New York: United Nations, 2010.
4 WHO, UNICEF, UNFPA, The World Bank. Trends in maternal mortality: 1990 to 2008. WHO, UNICEF, UNFPA, and The World Bank Estimates, 2010.
5 Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet* 2010; **375:** 1609–23.
6 Wilmoth J, Mathers C, Say L, Mills S. Maternal deaths drop by one-third from 1990 to 2008: a United Nations analysis. *Bull World Health Organ* 2010; **88:** 718.
7 WHO. International Classification of Diseases and Related Health Problems. Geneva: World Health Organization, 1992.
8 Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; **367:** 1066–74.
9 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2095–128.
10 United Nations. Millenium Development Indicators: world and regional groupings. http://mdgs.un.org/unsd/mdg/Host.aspx?Content=Data/RegionalGroupings.htm (accessed Feb 28, 2014).
11 WHO. WHO mortality database: tables. 2010. http://www.who.int/healthinfo/morttables.
12 Gulmezoglu AM, Say L, Betran AP, Villar J, Piaggio G. WHO systematic review of maternal mortality and morbidity: methodological issues and challenges. *BMC Med Res Method* 2004; **4:** 16.
13 WHO. ICD-10 translator. http://www.icd10data.com/Convert (accessed April 30, 2014).
14 WHO. The WHO Application of ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD-MM, 2012.
15 WHO, UNICEF, UNFPA, The World Bank. Trends in maternal mortality: 1990 to 2010. World Health Organization, UNICEF, UNFPA, and The World Bank, 2012.
16 Wilmoth JR, Mizoguchi N, Oestergaard MZ, et al. A new method for deriving global estimates of maternal mortality. *Stat Politics Policy* 2012; **3:** 1038.
17 R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing, 2011.
18 Plummer M. JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling. Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003); 2003; Vienna, Austria; 2003.
19 Abouzahr C, Royston E. Maternal mortality: a global factbook. Geneva: World Health Organization, 1991.
20 Ahman E, Shah IH. New estimates and trends regarding unsafe abortion mortality. *Int J Gynaecol Obstet* 2011; **115:** 121–26.

21 Gerdts C, Vohra D, Ahern J. Measuring unsafe abortion-related mortality: a systematic review of the existing methods. *PloS one* 2013; **8:** e53346.

22 Walker D, Campero L, Espinoza H, et al. Deaths from complications of unsafe abortion: misclassified second trimester deaths. *Reprod Health Matters* 2004; **12:** 27–38.

23 Chandramohan D, Setel P, Quigley M. Effect of misclassification of causes of death in verbal autopsy: can it be adjusted? *Int J Epidemiol* 2001; **30:** 509–14.

24 Leitao J, Chandramohan D, Byass P, et al. Revising the WHO verbal autopsy instrument to facilitate routine cause-of-death monitoring. *Glob Health Action* 2013; **6:** 21518.

25 Bouvier-Colle MH, Varnoux N, Costes P, Hatton F. Reasons for the underreporting of maternal mortality in France, as indicated by a survey of all deaths among women of childbearing age. *Int J Epidemiol* 1991; **20:** 717–21.

26 Deneux-Tharaux C, Berg C, Bouvier-Colle MH, et al. Underreporting of pregnancy-related mortality in the United States and Europe. *Obstet Gynecol* 2005; **106:** 684–92.

27 Kao S, Chen LM, Shi L, Weinrich MC. Underreporting and misclassification of maternal mortality in Taiwan. *Acta Obstet Gynecol Scand* 1997; **76:** 629–36.

28 Karimian-Teherani D, Haidinger G, Waldhoer T, Beck A, Vutuc C. Under-reporting of direct and indirect obstetrical deaths in Austria, 1980-98. *Acta Obstet Gynecol Scand* 2002; **81:** 323–27.

29 Schuitemaker N, Van Roosmalen J, Dekker G, Van Dongen P, Van Geijn H, Gravenhorst JB. Underreporting of maternal mortality in The Netherlands. *Obstet Gynecol* 1997; **90:** 78–82.

30 Centre for Maternal and Child Enquiries. Confidential enquiry into maternal and child health. Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2003–2005. The Seventh Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. Dec, 2007. http://www.publichealth.hscni.net/sites/default/files/Saving%20Mothers'%20Lives%202003-05%20.pdf (accessed April 15, 2014).

31 Lopman B, Cook A, Smith J, et al. Verbal autopsy can consistently measure AIDS mortality: a validation study in Tanzania and Zimbabwe. *J Epidemiol Community Health* 2010; **64:** 330–34.

32 Naghavi M, Makela S, Foreman K, O'Brien J, Pourmalek F, Lozano R. Algorithms for enhancing public health utility of national causes-of-death data. *Popul Health Met* 2010; **8:** 9.

33 Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2163–96.

34 WHO. The International Classification of Diseases 11th Revision is due by 2017. http://www.who.int/classifications/icd/revision/en/ (accessed Feb 28, 2014).

35 WHO. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization, 2012.

36 Duley L, Gulmezoglu AM, Chou D. Magnesium sulphate versus lytic cocktail for eclampsia. *Cochrane Database Syst Rev* 2010; **9:** CD002960.

37 Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2010; **11:** CD000025.

38 Duley L, Henderson-Smart DJ, Chou D. Magnesium sulphate versus phenytoin for eclampsia. *Cochrane Database Syst Rev* 2010; **10:** CD000128.

39 Duley L, Henderson-Smart DJ, Walker GJ, Chou D. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev* 2010; **12:** CD000127.

40 WHO. WHO Model List of Essential Medicines, 2013. http://www.who.int/medicines/publications/essentialmedicines/en/ (accessed April 29, 2014).

41 Aaserud M, Lewin S, Innvaer S, et al. Translating research into policy and practice in developing countries: a case study of magnesium sulphate for pre-eclampsia. *BMC Health Serv Res* 2005; **1:** 68.

42 Souza JP, Gulmezoglu AM, Vogel J, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. *Lancet* 2013; **381:** 1747–55.

43 WHO. Global status report on noncommunicable diseases 2010, 2011. http://www.who.int/nmh/publications/ncd_report2010/en/ (accessed April 30, 2014).

44 Bustreo F, Say L, Koblinsky M, Pullum TW, Temmerman M, Pablos-Mendez A. Ending preventable maternal deaths: the time is now. *Lancet Glob Health* 2013; **1:** 176–77.