Maternal mortality 1990 to 2015: A systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors 2015 Study

GBD 2015 Maternal Mortality Collaborators

Introduction

The global community adopted a set of 17 Sustainable Development Goals (SDGs) on September 25, 2015, to provide benchmark targets for global development between 2015 and 2030[1]. These goals are intended to build on the momentum and enthusiasm generated by the Millennium Development Goals (MDGs)[2], but also to reframe them within the context of myriad environmental and societal challenges inherent in achieving sustainable global development[3,4]. The Global Strategy for Women's, Children's, and Adolescents' Health 2016–2030 further aims to position the global discussion of maternal mortality within a continuum of programs aimed at improving the health of women and children globally[5].

As the MDG era has now come to a close and the SDG era is beginning, it is imperative to provide a comprehensive account of global, regional, and national progress toward MDG 5. Such information is of crucial importance to identifying areas of success and remaining challenges, and helping frame policy discussions as we continue to prioritise maternal and reproductive health for women in the SDG era[6]. Whereas MDG 5 set a target reduction of 75% in the maternal mortality ratio (MMR; number of maternal deaths per 100,000 live births) between 1990 and 2015, SDG 3.1 sets a specific target for all countries to lower MMR to less than 70 by 2030. A secondary target of MDG 5, adopted in 2005, called for universal access to reproductive health care with named sub-targets for contraceptive prevalence, adolescent pregnancy, antenatal care coverage, and family planning services[7], but notably not for other reproductive health services such as skilled birth attendance, in-facility delivery, or emergency obstetric care (EmOC) services. Because of its late addition to the MDG agenda, however, data collection systems have taken time to mature and reproductive health access has not been tracked as closely as maternal mortality. SDG 3.7 has continued the calls for universal access to sexual and reproductive health services by 2030.

We have completed this study as part of GBD 2015, with the specific objective of ascertaining levels and trends in maternal mortality over the entire MDG period at the national, regional, and global levels. Relatedly, by also examining maternal mortality trends by age, cause, geography and timing of death, we seek to better understand trends in maternal mortality epidemiology and thus generate insight into drivers of progress—or lack thereof—toward achievement of MDG 5 and help frame discussions for monitoring of SDG 3.1 and 3.7. Multiple previous analyses, including several completed as part of the Global Burden of Diseases, Injuries, and Risk Factors (GBD) collaboration, have sought to provide the best possible information on levels and trends in maternal mortality[8–14]. In dual recognition of both the importance and difficulty of accurately reporting on maternal mortality in many settings[15,16], each has incorporated increasingly large and geographically precise datasets and utilized more advanced statistical models. In their latest iteration[12], the World Health Organisation (WHO) methods have also now adopted a single model for all countries and computed statistical uncertainty intervals. Important differences remain, however, between WHO and GBD maternal mortality estimates that at times paint divergent pictures of levels and trends in maternal mortality globally and in many countries. The main differences now stem from data selection, quality appraisal, data processing, and adult mortality estimation rather than the statistical maternal mortality models themselves.

In this GBD 2015 report, we present the underlying data for 519 distinct geographic units in 195 countries and territories, our methods for processing those data, the subsequent analytic approach, and findings on maternal mortality from 1990 to 2015. Published in 2012, GBD 2010 presented results for 187 countries with a population greater than 50,000 in the year 2000.[17] Collaborative teams completed subnational assessments for the United Kingdom, Mexico, and China for GBD 2013, expanding the number of geographies in the GBD analysis to 296.[18–21] The value of subnational assessments to local decision-makers[22] has led to expansion of subnational analyses in GBD 2015 to also include Brazil, India, Japan, Kenya, Saudi Arabia, South Africa, Sweden, and the United States. We expect subnational analyses for other countries will be added in future GBD iterations. The expansion of the geographical units in the GBD will continue in a way that will sustain comparability over time for the period 1990 to present and across all geographic entities. We have not included constant rate-of-change forecasts in this paper because, as part of the broader effort to quantify the population disease burden, we are developing a set of rigorous statistical models to forecast each component of the GBD—including maternal mortality—and we expect to be able to explore much more robust forecasts in the near future.

As with all GBD revisions, the GBD 2015 study describes updated maternal mortality estimates for the entire time series from 1990 to 2015 based on newly identified data sources released or collected since GBD 2013. In response to published commentaries and unpublished seminars and communications on GBD methods, various methodological refinements have been implemented[23,24]. In addition, a major effort toward data and code transparency has been part of the GBD 2015 cycle. And as with each GBD cycle, the full time series published here supersedes prior GBD studies. This analysis explores global, regional, national, and subnational progress and seeks to identify correlates that help explain why some nations have seen great improvements in maternal health while others have stagnated and others still have worsened. These include examination of associations in national maternal mortality levels and trends with coverage of reproductive health interventions and Socio-Demographic Index (SDI).

Methods

Overview

Maternal mortality is defined as a death that occurs to a woman as a direct result of obstetric complications or indirectly as a result of pregnancy-induced exacerbation of pre-existing medical conditions, but not as a result of incidental or accidental causes. To ensure internal consistency with all other causes of death, maternal mortality was again analysed as a component of the overall GBD study. Many of the analytic components are therefore shared with other causes, including methods of data source identification and cataloguing, data preparation, modeling platforms, and processing of results. Here we will focus on parts of the process that are unique, have been updated since GBD 2013, or are especially relevant to our analysis of maternal mortality. Figure 1 illustrates details of the analysis. General components are described in the appendix, in other reports in this issue, and have also been published previously[10,25,26]. This report follows the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) guidelines proposed by WHO and others which provide recommendations on documentation of data sources, methods, and analysis[27].

Maternal mortality estimation

Geographical units of analysis

Our analysis was completed separately for 519 unique locations in 195 countries and territories. This includes all 188 countries analysed in GBD 2013 as well as seven additional countries or territories, namely American Samoa, Greenland, Guam, Northern Mariana Islands, Puerto Rico, and the US Virgin Islands, where high-quality vital registration (VR) data were available. Of note, these territories were not included in the national totals for Denmark, the United Kingdom, or the United States, but were instead included in GBD 2013 regional totals. All 195 countries are hierarchically organized into 21 regions, each of which is nested in one of seven super-regions. Based on a combination of data availability and collaborator interest, we disaggregated GBD 2015 analyses into subnational units for a number of countries, including 26 states and one district for Brazil, 34 provinces and municipalities for China, 31 states and union territory groupings for India that include 62 rural and urban units, 47 prefectures for Japan, 47 counties for Kenya, 32 states and districts for Mexico, 13 provinces for Saudi Arabia, nine provinces for South Africa, two regions for Sweden, 13 regions for the United Kingdom (Northern Ireland, Scotland, Wales, England, and nine sub-regions of England), and 51 states and districts for the United States. At the first subnational unit level, we have a total of 256 geographic units. In this paper we present results for countries and territories, regions, super-regions, SDI quintiles, and at the global level.

Data input and processing

The contents of the dataset used in our final model are shown in Table 1 and compared to those used by the recent WHO analysis[12]. The data coverage by location for all source types combined is mapped in Figure 2. We had 599 unique sources from data from 186 of 195 countries (95%), covering 12,052 site years, an increase of 71% from GBD 2013 when we had 7,056 total site years of maternal mortality data. The nine countries without maternal mortality data included Andorra, Angola, Equatorial Guinea, the Federated States of Micronesia, Marshall Islands, Samoa, Solomon Islands, Somalia, and Vanuatu. Maternal mortality data were also available for additional subnational locations in Mexico, China, the United Kingdom, Japan, the United States, Kenya, South Africa, India, Sweden, and Brazil. All data were stored in a centralized SQL causes-of-death (COD) database in three formats: number of deaths, cause-specific mortality rate per capita (CSMR), and cause fraction (CF; proportion of all deaths due to maternal causes).

Vital registration (VR) systems have been shown to underestimate maternal mortality, but the amount of underestimation varies by setting and may change over time[22–24]. We therefore used a method that maximizes the data-driven nature—and specificity—of our adjustments by systematically evaluating each underlying data source. We included all sources with population-level data on maternal mortality from each geography. We used a standardized process to identify, extract, and process all relevant data sources, including those from VR systems, verbal autopsy (VA) studies, maternal surveillance systems, national confidential enquiry reports, and sibling survival histories from health surveys and censuses (Figure 1, Step 1).

Standardized algorithms were implemented to adjust for age-, year-, and geography-specific patterns of incompleteness and underreporting for VR, as well as patterns of misclassification of deaths in VR and VA sources (Figure 1, Step 2). These generalized algorithms were employed across all GBD causes and thus were able to capture trends in VR quality changes with respect to maternal mortality even in

locations where surveillance studies have not been completed[25]. Each code in ICD-coded VR datasets was uniquely assigned to a corresponding cause in the hierarchical GBD cause list. Codes used in tabular classification systems (e.g., ICD-9 BTL [Basic Tabular List], verbal autopsy, maternal surveillance systems) were likewise uniquely matched with a GBD cause. A proportion of deaths assigned to causes that cannot be underlying causes of death (garbage coded) were reassigned to maternal causes based on statistical redistribution packages, as described in the appendix. The net effect of data processing steps on VR across all locations and years combined was to increase maternal deaths by 168%. The net effect varied by geography and year even amongst those countries and territories with at least 10 years of data, ranging from <1% increase in Mongolia to a 9-fold increase in China. Final and raw VR data for each country and year are shown in the appendix, including proportion of all deaths assigned to garbage codes, and comparisons with WHO VR adjustments[12]. Figure 3 graphically illustrates the results of garbage code redistribution for maternal mortality at the global level. Distinct cause groupings, many of which are garbage codes, are shown on the left and the relative thickness of lines shows the proportion of all deaths from those codes that were subsequently mapped to corresponding maternal causes on the right. Note that by definition the "non-garbage" codes on the left map directly to maternal causes.

Given their inconsistent use by VR systems, codes pertaining to HIV-related indirect maternal deaths were excluded at this stage in favor of a more comprehensive approach to estimating the impact of HIV on maternal death (see below for more details of HIV-related maternal mortality analysis). In addition to VR, we identified maternal mortality surveillance systems and published confidential enquiry (CE) studies identified via targeted web search and systematic review of national ministry of health websites. CE are specialised studies designed to investigate the number and circumstances of maternal deaths. Inclusion required a clear distinction identified between maternal and incidental deaths during pregnancy. As with VR systems, HIV-related indirect maternal deaths were excluded from surveillance datasets at this stage (see below for more details) but otherwise were unadjusted. Single-year sibling history and survey data derived from health surveys and censuses was processed as in GBD 2013, using Gakidou-King weights to adjust for survivor bias and only retaining data from older surveys when years of death overlapped[28] (Figure 1, Step 3).

Our general approach to quantifying the role of HIV in maternal mortality is unchanged from GBD 2013 and again involved comprehensive estimation of the population-attributable fraction (PAF) of maternal mortality to HIV[10] (Figure 1, Step 4). Given the increased baseline mortality of those with advanced HIV, this approach has helped distinguish between deaths in HIV-positive women that were caused by pregnancy and those for which the pregnancy was incidental to their death. A detailed description of the GBD 2013 approach and updates is in the appendix. An updated systematic literature search completed on July 20, 2015, did not reveal any new sources to inform either our meta-analysis of relative risk of pregnancy-related death for HIV-positive versus HIV-negative women or our analysis on the proportion of pregnancy-related deaths in HIV-positive women that are maternal (versus incidental). HIV prevalence in pregnancy, approximated as the ratio of live births in HIV-positive to HIV-negative women, was updated using our modified EPP-Spectrum model. We also made two important improvements to overall HIV mortality estimation, both of which impacted our HIV-related maternal mortality estimates. First, to improve the internal consistency of estimates developed for countries with generalised HIV epidemics, we modified EPP-Spectrum to improve how it integrates ART-dependent HIV progression and mortality data from published cohort studies and combined these findings with results derived from statistical examination of how all-cause mortality relates to crude HIV death rate. Second, in recognition

of the fact that HIV mortality rivals or exceeds that of high mortality events (referred to as "fatal discontinuities" in GBD 2015) such as war and natural disaster in many locations—and that such discontinuities have significant detrimental effects on statistical mortality models—all of our maternal mortality data were processed to ensure incidental HIV deaths were excluded prior to modeling. We processed sibling history and census data to exclude incidental HIV deaths using PAFs calculated above for each geography, age group, and year. This is analogous to the HIV-correction process used in GBD 2013 except that the correction was performed on the data itself rather than the preliminary model results. To ensure consistency between all data sources, we also applied PAFs to all VR, VA, and surveillance data to add back the corresponding number of HIV-related indirect maternal deaths in each of those sources. Finally, to reduce error introduced by large stochastic fluctuations and upward bias introduced by data that have a value of zero , we processed all data of all specifications using Bayesian noise-reduction algorithms – see appendix for more details (Figure 1, Step 5). Zeros are problematic because the log of zero is undefined, so all zeroes would otherwise be ignored by log-based statistical mortality models.

Modelling overall maternal mortality

We again modeled overall maternal mortality using cause-of-death ensemble modeling (CODEm), which was developed for GBD 2010[29] and is described in detail in the appendix (Figure 1, Step 6). CODEm runs four separate models, including natural log of age-specific death rates and logit-transformed cause-fractions in each of linear and spatiotemporal Gaussian process regression (ST-GPR) formats. Using multiple holdout patterns and cross-validation testing, every combination of covariates was tested. Models where regression coefficients met requirements for direction and significance were then ranked on the basis of out-of-sample predictive validity performance through multiple iterations of cross-validation testing. We then generated a series of ensemble models with a range of weightings such that top-performing component models contributed the most to the final prediction. We ran two separate CODEm models, one for countries with extensive complete VR representation and another for all countries combined. The purpose was so that heterogeneous data from countries without extensive complete VR representation would not inflate the uncertainty interval for countries with extensive and complete cause-specific death data. Results from the former model were used for all geographies with extensive complete VR representation; results for all other geographies were from the latter model.

Predictive covariates were specified with respect to required directionality and significance level of regression coefficients (see appendix for full details). Three hierarchical covariate levels reduce the combinatorial burden on CODEm. Covariates with strong or causal association were assigned to level 1; those that are ecologically related were assigned to level 2; and those where association is suspected but not proven at the population level were assigned to level 3. We largely used the same covariates as in GBD 2013, including age-standardised fertility rate, total fertility rate, years of education per capita, lag-distributed income (dollars per capita), neonatal mortality rate (per 1,000 live births), HIV mortality in females of reproductive age, and the coverage proportion of one visit of antenatal care, four visits of antenatal care, skilled birth attendance, and in-facility delivery. Several new covariates were introduced in this analysis in recognition of their potential relationship to maternal mortality, all of which were specified as level 3. Obesity prevalence was added to help reflect the added complexity of care and heightened risk of maternal complications in those who are obese[30,31]. Mortality death rate from fatal discontinuities, a covariate that aggregates the effects of war, famine, and natural disaster, was introduced to help inform maternal mortality estimates in geographies where demographic shocks have

led to interruption of vital statistics and where health systems are also hypothesized to have deteriorated[32,33]. Hospital beds per 1,000 population was added based on the hypothesis that it may be a proxy for the availability of basic emergency obstetric care[34]. Socio-Demographic Index (SDI), based on principal component analysis of fertility, maternal education (years per capita), and lag-distributed income (International $ per capita), was added as a covariate to all CODEm models in GBD 2015. The root-mean standard error of the top-performing ensemble model was 0.318 for the DR model and 0.553 for the global model. In-sample and out-of-sample data coverage was 99.6% and 99.3%, respectively, for the DR model. It was 98.3% and 97.7%, respectively, for the global model. The relative contributions of each of the covariates and sub-model performance for all component models in the top-performing CODEm ensemble are shown in Appendix Table 4.

Modelling underlying etiology and timing of maternal mortality

Our approach for quantifying underlying etiology and timing of maternal deaths was largely unchanged from GBD 2013, although in some cases we changed cause names to better reflect the ICD-9 and ICD-10 codes contained therein. ICD-9 and ICD-10 codes corresponding to each category are in the appendix. We examined six groups of direct obstetric causes including maternal hypertensive disorders; maternal haemorrhage; maternal abortion, miscarriage, and ectopic pregnancy; maternal obstructed labor and uterine rupture; maternal sepsis and other maternal infections; and other maternal disorders. Two categories of indirect obstetric causes included maternal deaths aggravated by HIV/AIDS and indirect maternal disorders. Late maternal deaths occurring between 42 days and 1 year after the end of pregnancy were estimated as a separate etiology (ICD-10 code = O96). There are two notable differences between the GBD and ICD-MM classification systems, neither of which are new in this study, but nonetheless warrant mention in that they each reflect important clinical aspects of pregnancy complications. First, the GBD has grouped uterine rupture with obstructed labor rather than maternal haemorrhage, in recognition that a majority of uterine rupture cases are secondary to inadequately addressed or prolonged obstruction of labor. Second is the combining of abortion, ectopic pregnancy, and miscarriage into a single cause. Although there are important differences between them, safe treatment is similar for each condition during early pregnancy (e.g. medication, potentially dilation and evacuation) and in managing life-threating complications such as infection and bleeding (e.g. infection, bleeding) which require prompt evaluation, diagnosis, and often emergency surgical intervention. We also examined four distinct time windows of maternal death. In addition to late maternal deaths, we estimated deaths occurring during the antepartum period (prior to onset of labor), intrapartum and immediate postpartum (onset of labor up to <24 hours after delivery), and early and delayed postpartum (24 hrs to 42 days after delivery). We analysed late maternal death as both a timing category and as a distinct etiology because the underlying causes of late maternal deaths are not specified in most data sources.

Systematic literature reviews identified studies that examined underlying causes and timing of maternal deaths (Figure 1, Step 7). We extracted additional information from specialized studies such as confidential enquiries and maternal mortality review boards that were obtained from targeted web searches or from correspondence with GBD collaborators. We supplemented etiology models with cause-specific data from the causes-of-death (COD) database. Of note, our criteria for including data from the COD database was modified from GBD 2013 to include all data from any source where specific sub-causes were coded rather than limiting to only those sources where the complete complement of sub-causes were included. This change had the effect of dramatically increasing the size of our analytic

dataset with respect to time and geography. Late maternal death data from the COD database were limited to those location-years where at least 0.5% of all maternal deaths in raw VR data files were coded to late maternal deaths as this was the lowest proportion reported in any surveillance studies[35]. Only 39 countries met these criteria with variable times in which they began coding late maternal deaths. Timing models were additionally supplemented with temporal information on pregnancy-related deaths from DHS maternal mortality modules. These data only reported on antepartum, intrapartum, and postpartum death.

In order to maximize the volume and geographic distribution of data to inform etiologic attribution, we again modeled the proportion of deaths due to each etiology and timing category using DisMod-MR 2.1 (Figure 1, Step 8). The exception was HIV-related maternal mortality, where the proportion was estimated using the PAF approach described above (Figure 1, Step 9). All data for etiology and timing models where late maternal death was excluded were statistically cross-walked within DisMod-MR 2.1 to the reference definition where late maternal death is included. Analytic details of DisMod-MR have been previously described[10]. Further description, including details about updates contained in DisMod-MR 2.1 and statistical cross-walks, are also included in the appendix. To correct for ascertainment bias inherent in the introduction of late maternal death partway through the MDG period, we corrected overall maternal mortality estimates for the systematic exclusion of late maternal death in those location-years where it was not coded (Figure 1, Step 10). Selection criteria for identifying those geographies and years to be corrected is described above. Geographies where coding of late maternal deaths was introduced partway through the time period were only corrected for the years prior to introduction. Age-, year-, and geography-specific proportions predicted by DisMod-MR 2.1 for underlying etiologies and timing were then applied to the overall maternal mortality model developed in CODEm (Figure 1, Step 11).

Ensuring consistency with all other causes of death

Another crucial strength of the GBD approach to maternal mortality is that all results are internally consistent with all other specific causes of death (Figure 1, Step 12). CoDCorrect is a process that employs a simple algorithm to scale all cause-specific deaths from all causes for each age-group, sex, year, and location and thereby ensures that the sum equals total all-cause mortality. For maternal mortality, it further scaled the sum of all etiology-specific and timing-specific estimates to equal the total for all maternal mortality. Further details on CoDCorrect and its implementation are described in the appendix.

Age groups and fertility

Previous analyses have truncated evaluation of maternal mortality at 15 to 49 years. Doing so ignores the non-trivial number of pregnancies and deaths occurring in those less than 15 and more than 50 years old[36]. Deaths in these age groups are routinely coded in our data sources, so for the first time, we have expanded the age range of our maternal mortality analysis to include all five-year age groups from 10 to 54 years in GBD 2015. To facilitate calculation of MMR in these age groups, our demographic analysis included expansion of UN Population Division estimates of age-specific live births to include 10-14 years and 50-54 years (Figure 1, Step 13). The appendix provides more detail on fertility estimation in these age groups and a table of age-specific live births for all locations.

Uncertainty analysis

We report 95% uncertainty intervals (UIs) for all estimates. UIs include uncertainty introduced by variable sample sizes, data adjustments for all-cause mortality sources, and cause-specific model specifications and estimation. In CODEm, after a model weighting scheme has been chosen, each model contributes a number of draws proportional to its weight such that 1,000 draws are created. The mean of the draws is used as the final estimate for the CODEm process and 95% UI are created from the 0.025 and 0.975 quantiles of the draws. In DisMod-MR 2.1, uncertainty is calculated by sampling 1,000 draws from the posterior distribution of each most-detailed geography, age group, and year. UIs for underlying etiologies and timing are propagated from the combination of CODEm and DisMod-MR 2.1 draws. We propagated uncertainty into all the final quantities of interest at all levels of geographic, temporal, and age-specific aggregation assuming no correlation between them.

Analysis of levels and trends

MMR, annualised rate of change, and reporting metrics

We report number of deaths and maternal mortality ratio (MMR; number of deaths per 100 000 live births) for ages 10 to 54 inclusive. We calculated MMR for each five-year age group separately using age-specific live births (Figure 1, Step 14). We calculated annualised rate of change (ARC) using the two-point continuously compounded rate-of-change formula[37] in each geography separately for 1990 to 2000, 2000 to 2015, 1990 to 2015, and all single years throughout the time period. ARC examination reveals overall trends, highlights periods of acceleration (or deceleration) in improvement, and permits identification of those countries that likely achieved MDG 5.

Drivers of change in the MDG era, coverage target setting for SDGs

For GBD 2015, we completed two additional analyses to systematically describe drivers of levels and trends in maternal mortality. First, we examined the relationship between MMR and the Socio-Demographic Index (SDI), a summary indicator derived from measures of income per capita, educational attainment, and fertility using the Human Development Index methodology[38]. The SDI has an interpretable scale: zero represents the lowest income per capita, lowest educational attainment, and highest TFR observed across all GBD geographies from 1980 to 2015 and one represents the highest income per capita, highest educational attainment, and lowest TFR. We then used spline regression to calculate the average relationship between MMR and SDI, thereby facilitating further evaluation of geographic and temporal MMR trends. Further details of SDI development and spline regressions are in the appendix. We then used the average relationship between SDI and MMR to calculate observed minus expected (O-E) MMR ratio and O-E ARC (from 2000 to 2015), respectively, to show average patterns that can help benchmark a country against other countries and provides insights into whether or not public action or other factors have been leading to narrowing—or growing—inequalities since the MDG declaration. , Second, to capture how improvements in women's access to the specific modes of reproductive health care may alter the average relationship observed between SDI and MMR, we also examined the relationship between MMR and coverage of one visit of antenatal care (ANC), four ANC visits (a proxy for more comprehensive care), in-facility delivery (IFD), and skilled birth attendance (SBA) by calculating the average coverage of each over different MMR ranges.

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

Results

Global and country-specific maternal mortality

Global maternal deaths decreased slightly from 390,185 (95% UI: 365,193– 16,235) in 1990 to 374,321 (351,336 – 400,419) in 2000 before dropping to 275,288 (243,757– 315,490) in 2015 as shown in Figure 4. The overall decrease from 1990 to 2015 in global maternal deaths was roughly 29% and the decrease in MMR was 30%. Results for all specific geographies in the GBD hierarchy are shown in Table 2. MMR followed a similar trend to overall maternal deaths. It was 282 (264 – 300) in 1990, 288 (270 – 308) in 2000, and decreased to 196 (173 – 224) in 2015. Global ARC was -1.5% (-2.0 – -0.9%) across the entire MDG period from 1990 to 2015. It was initially relatively flat at 0.21% (-0.46 – 0.87%) from 1990 to 2000, but accelerated significantly after the Millennium Declaration to be -2.6% (-3.4 – -1.7%) from 2000 to 2015. Looking at single-year ARC, we see the global acceleration began in the year 2001 and has continued accelerating until 2007–2008, after which the rate of improvement has slowed.

Geographic differences in maternal mortality are readily apparent. As shown in the map from 1990 in Figure 5a, 60 countries had an MMR greater than 200, 40 countries had an MMR of greater than 400, and 15 greater than 600. Only 1 country—Burundi —had an MMR greater than 1,000. MMR was less than 70 in 93 countries at that time. A subset of 50 had MMR of less than 30, and 28 were less than 15. By the year 2015, as shown in Figure 5b, 122 countries had an MMR of less than 70, and 49 had an MMR of less than 15, including Saudi Arabia, all countries in central Europe, and all high- income locations with the exception of the United States, Argentina, Brunei, Chile, and Uruguay. Several other countries in North Africa and Middle East along with the United States, Armenia, Azerbaijan, Bulgaria, Chile, China, Costa Rica, Kazakhstan, Puerto Rico, Romania, Russia, Tajikistan, Thailand, Turkmenistan, Ukraine, Uruguay, Uzbekistan, and Vietnam had MMR between 15 and 30. Unfortunately, there were still 24 with MMR of greater than 400, 8 greater than 600, and still one—Central African Republic--greater than 1,000. Of those greater than 600, Sierra Leone, Afghanistan, and Central African Republic actually worsened, with ARC from 1990 to 2015 of 2.7% (-1.3 – 6.3%), 0.34% (-2.1 – 2.7%), and 0.08% (-5.5 – 4.9%), respectively. Of those with an MMR higher than 400 in 1990, Burundi and Equatorial Guinea improved substantially by 2015 with total improvements of -4.3% (-8.7 – .3%) and -4.2% (-9.6 – 3.9%), respectively.

MDG 5 achievement

In order to achieve the primary objective of MDG5, ARC must have met or exceeded an average of -5.5% over the entire time period from 1990 to 2015. Based on this metric, a total of ten countries likely achieved MDG5, including Iceland, Jordan, Maldives, Belarus, Morocco, Romania, China, Turkey, Poland, and Estonia. A number of other countries achieved this rate of improvement at some point during the MDG period. From 2000 to 2015, a total of 24 countries exceed ARC of -5.5%. Many countries, despite not achieving the ambitious MDG 5 target of a 75% reduction, actually have been experiencing steady declines in maternal mortality for quite some time. One hundred forty-eight of 195 countries and

territories saw their peak MMR occur before the year 2000, with an additional 21 occurring by the year 2005. Maternal mortality increased in 26 countries between 1990 and 2015.

The relationship between MMR, SDI, and reproductive health services

Figure 6 shows global and regional-level MMR and SDI from 1990 to 2015. The black convex line represents the average relationship between MMR and SDI over the time period and is the basis of "expected" MMR. Maternal mortality in the lowest SDI quintile improved the least, with ARC of only -0.97% (-1.8 – -0.001%) from 1990 to 2015, and the low-middle SDI quintile was the next slowest with an ARC of -2.1% (-2.8 – -1.1%). The proportion of all maternal deaths occurring in the bottom two SDI quintiles increased from roughly 68% in 1990 to more than 80% in 2015. The middle SDI quintile improved the fastest with ARC of -3.2% (-3.8 – -2.6%) over the entire time period (Table 2). Each colored symbol represents a successive year from 1990 to 2015 for the global level and GBD regions. At the global level, MMR in 2015 was more than double what would have been predicted solely by average SDI. This was following a period from 1990 to 2000 where global MMR improved more slowly than would have been expected based on SDI improvement and a period of faster-than-expected MMR improvement from 2000 to 2015. Based on the expected relationship between MMR and SDI, reaching the SDG 3.1 achievement threshold of MMR 70 would require an SDI of 0.65, corresponding to an average income of roughly $9,442 per capita, 8.2 years of education, and total fertility rate (TFR) of 2.5. Not all countries may be able to achieve that level of income, however, but education and fertility reduction efforts may still be compatible with reaching this SDI level. If all women were to complete a full 12 years of education and TFR of 2.7, an SDI of 0.65 would on average be associated with income of $3,214 per capita. If TFR were to decrease further to the population replacement rate of to 2.0 and education were 12 years, this SDI level would only require an annual income of $2,648 per capita.

MMR and SDI both improved between 1990 and 2015 in almost all regions, but MMR did not universally track with SDI over the entire time period in any single region. East Asia has had the lowest O-E MMR ratio since 2011, a period in which it has consistently been less than 0.4 of expected. Australasia has also had consistently lower MMR than would be predicted on the basis of SDI, with O-E MMR ratio ranging from 0.54 in 1990 to 0.71 in 2015. In addition to East Asia and Australasia, several other regions have consistently had lower MMR than would have been expected by SDI, including central Asia, central Europe, eastern sub-Saharan Africa, Western Europe, and high-income Asia Pacific. Southern Latin America and North Africa and the Middle East both had lower than expected MMR in 1990 when both had O-E MMR ratios of <0.7, but improvement has not kept pace with SDI gains in either region: by 2015, O-E MMR ratios were 2.23 and 1.41, respectively. Central sub-Saharan Africa has been an exception in multiple ways. In addition to having the highest MMR of any region in 2015, MMR worsened from 1990 to 2015. Despite maternal mortality being high in central sub-Saharan Africa, it was still lower than would have been expected until 2014 because SDI is still so low in that region and has improved only slowly.

O-E MMR ratio has consistently been 1.25 or more in a larger number of regions, including the Caribbean, Eastern Europe, high-income North America, Oceania, South Asia, Southeast Asia, and southern sub-Saharan Africa. Andean Latin America had periods of rapid improvement in MMR during the early 2000s that exceeded that expected based on SDI. Unfortunately, MMR reductions there have slowed considerably since then, to the point where O-E MMR ratio was 1.41 in 2015. Improvements in Eastern Europe have been faster than SDI after the year 2000, but MMR improvement in the remaining regions has continued to be slower than expected on the basis of SDI. Southern sub-Saharan Africa and

the Caribbean had the highest O-E MMR ratios of any regions at 3.57 and 3.71, respectively, in 2015, but both have had recent periods of MMR improvement that were much more rapid than expected on the basis of SDI. These trend reversals began in 2006 and 2007, respectively. South Asia and Southeast Asia are unique in that while both have made dramatic gains in terms of SDI and MMR, the difference between observed and expected MMR based on SDI remained the same.

Even within regions, the degree to which MMR diverged on the basis of SDI varied. For each country, we calculated observed ARC minus expected ARC (O-E ARC) on the basis of SDI change from 2000 to 2015 (Figure 7). There were a total of 60 countries where O-E ARC was faster than would have been expected based on SDI alone, and 25 of these had ARC at least 1.5% faster than expected. Within South Asia, Bangladesh has improved faster than expected while Nepal, Bhutan, and India all had slower MMR reductions. Of the countries in Southeast Asia, Cambodia and Laos have improved much faster than expected while Thailand, Philippines, and Malaysia have not. In sub-Saharan Africa, Namibia, Malawi, and Burundi were all more than 1.5% faster than expected, but ARC in most of the countries of eastern and western sub-Saharan Africa exceeded SDI-based expectations. In contrast, only Gabon in central sub-Saharan Africa reduced MMR as rapidly as expected, with Democratic Republic of the Congo and Equatorial Guinea both more than 3% slower. A total of 93 countries had O-E ARC of 1.5% or more, and there were 17 countries where O-E ARC was greater than 5%.

To begin exploring the hypothesis that MMR improvements are related to coverage of specific modes of reproductive health care, we examined the relationship between MMR and coverage of one visit of antenatal care (ANC), four ANC visits, in-facility delivery (IFD), and skilled birth attendance (SBA) over the period from 1990 to 2015 (Table 3). We found that, on average, countries with an MMR of less than 15 had 98% coverage of one ANC visit, 95% of four ANC visits, 97% of IFD, and 99% of SBA. Those with an MMR of 70—the SDG 3.1 target for all countries—have roughly 91% coverage of one ANC visit, 78% of four ANC visits, 81% of IFD, and 87% of SBA. This is in contrast to those countries with an MMR around 200 where there is an average of 84% coverage of one ANC visit, 61% of four ANC visits, 63% of IFD, and 70% of SBA, and those locations with an MMR over 500 where coverage of all services was low, including just 76% coverage of one ANC visit, 45% of four ANC visits, 41% of IFD, and 48% of SBA. Comparable datasets were not available to examine the relationship between MMR and coverage of either emergency obstetric care (EmOC), distance to obstetric care, post-natal care coverage, or family planning services such as modern contraception and access to safe abortion services.

Age pattern of maternal mortality and fertility

The risk of maternal mortality increases dramatically with age but decreased significantly in almost all age groups from 1990 to 2015 (Figure 8). At the global level in 2015, MMR in 10–14 year olds girls was 278 (229 – 339). MMR then decreased and was lowest in women from 15–29 years old before increasing dramatically to 1,832 (1,284 – 2,746) in 50- to 54-year-olds (not shown on graph). While the largest number of births still occur amongst women between the ages of 20 and 29 years (55% of total), there has been a decrease in adolescent fertility and a net shift in births to older women (Appendix Table 11 of live births). In 1990, 23.3 million (17% of total) live births occurred in those under the age of 20, and 0.58 million (0.42% of the total) were to girls aged 10-14 years. In 2015, 19.4 million (14% of total) births were in those 10 to 19 years old, but there were still 0.48 million (0.34% of total) to girls under the age of 15 years. In contrast, the absolute number of annual births to women ages 35 and older increased from 16.1 million (12% of total) in 1990 to 18 million (13% of total) in 2015. ARC in MMR among 10- to

19-year-olds from 2000 to 2015 was -2.3 (-3.3 – -1.2), which was slower than the global ARC in MMR for all ages combined.

Cause pattern of maternal mortality

Although the risk of death from all causes increases with age, a majority of deaths still occur in younger women and the absolute numbers of deaths from all causes except HIV are higher in younger age groups (Figure 9a-c). Direct obstetric causes accounted for approximately 86% of all maternal deaths at the global level in 2015, led by maternal haemorrhage, maternal hypertensive disorders, and other maternal disorders. This is down only slightly from 1990 when direct complications accounted for 87% of all maternal deaths. Other maternal disorders decreased the most of all etiologies between 1990 and 2015, from a total of 74,299 (61,159 – 89,653) deaths in 1990, down to 32,734 (26,256 – 40,507) deaths in 2015. Maternal abortion, miscarriage, and ectopic pregnancy, and maternal sepsis and other maternal infections were the etiologies with the next largest declines between 1990 and 2015. Indirect maternal disorders increased in importance from 1990 when they caused 42,246 (32,355 – 54,032) deaths (approximately 11% of total) to 2015 when they caused 33,108 (25,463 – 43,344) (approximately 12% of total). HIV-related maternal deaths were responsible for a portion of the increase in indirect maternal deaths, rising from 754 (433 – 1,095) globally in 1990, peaking in the year 2000, and coming down to 2,322 (1,394 – 3,337) in 2015; this was 0.84% of overall maternal mortality in 2015. 2,181 (1,306– 3,174) of HIV-related maternal deaths were in sub-Saharan Africa in 2015, roughly 1.6% of the total there. Overall, the contribution of HIV to overall maternal death was quite small, but there are a large number of pregnant and postpartum women dying from complications HIV/AIDS. If we include incidental HIV deaths during pregnancy from our PAF analysis, a total of 20,180 (12,120 – 29,005) HIV-positive women died while pregnant or postpartum in 2015. (Appendix Table 10 shows etiology-specific maternal deaths for all GBD locations.)

Changing cause pattern by age

The age pattern for underlying maternal mortality etiologies in 2015 (Figure 9d) shows that in the youngest age groups, maternal haemorrhage and maternal hypertensive disorders are the dominant causes, together accounting for over 50% of all maternal deaths. While the comparative risk associated with maternal hypertensive disorders decreases with age, haemorrhage actually peaked in importance in the 35 to 39 years old. The contribution of most other etiologies of maternal death also increased with age, especially other direct maternal disorders and the combined category of abortion, ectopic pregnancy, and miscarriage. Late maternal deaths decreased steadily in importance from 1990, when 8,460 (5,792 – 11,935) late maternal deaths occurred, to 2015, when 6,711 (4,335 – 9,996) occurred, and still was the time period with the smallest absolute number of deaths (Appendix Table 11 of timing deaths). The antepartum and postpartum periods were the periods with the largest numbers of deaths in 2015 at 101,774 (88,185 – 117,570) and 85,686 (72,956 – 101,862), respectively. The age pattern showed that the proportion of postpartum deaths peaked in the youngest age groups while intrapartum and antepartum deaths were more important in those over the age of 35 years (Appendix Figure 2). If we look at the change in underlying etiology patterns as predicted by SDI (Figure 10), we see that in the lowest SDI countries, maternal mortality is dominated by maternal haemorrhage. In high-SDI geographies, in contrast, the etiology pattern changes dramatically to one where other direct maternal disorders, indirect maternal disorders and abortion, ectopic pregnancy, and miscarriage are the most important causes of maternal death. In middle SDI countries, the epidemiological profile is even more

complicated, with a particularly high proportion of maternal deaths being due to maternal hypertensive disorders.

Discussion

Summary

The overall change from 1990 to 2015 in global maternal deaths was roughly -29% and in MMR -30%, both of which were well short of the MDG 5 goal of -75%. Global maternal deaths were largely unchanged from 1990 to 2000, decreasing only slightly from 390,185 (365,193 – 416,235) in 1990 to 374,321 (351,336 – 400,419) in 2000. Progress in MMR during the 1990s was also virtually undetectable when global ARC was only 0.21% (-0.46 – 0.87). This was 4.1% slower than would have been expected on the basis of SDI alone. After the Millennium Declaration, maternal mortality improvements accelerated. In 2015 there were 275,288 (243,757 – 315,490) maternal deaths, and average global ARC in MMR from 2000 to 2015 was -2.6% (-3.4% – -1.7%), although even with acceleration progress was 1.8% slower than would have been expected on the basis of SDI improvements alone.

Only ten countries achieved MDG 5 based on this analysis, including Iceland, Jordan, Maldives, Belarus, Morocco, Romania, China, Turkey, Poland, Estonia. Although overall progress has been slow during the MDG era, recent accelerations mean there are an additional 24 countries where ARC has met or exceeded the MDG 5 achievement rate between 2000 and 2015. There was significant variability in MMR throughout the world in 2015, ranging from a low of 0.8 (0.6 – 0.9) in Iceland to a high of 1,074 (215 – 2857) in Central African Republic. One hundred twenty-two of 195 countries had MMR in 2015 that is already less than the SDG 3.1 goal of 70.

Impediments to MMR reduction are multifaceted and variable; many are also well-conceptualised through the lens of our SDI analysis. First, slow improvement in the two lowest SDI quintiles is one of the primary reasons that maternal mortality reduction has been slower than expected at the global level. In 1990, these two quintiles collectively accounted for 68% of maternal mortality, but by 2015, increased to more than 80% of the global total. Part of the reason is that high adolescent fertility rates in these locations, coupled with comparatively slow improvement in adolescent MMR, led to concentration of maternal mortality burden in young women and girls and higher total fertility in these populations. Second, some middle SDI locations may be experiencing a period of inertia where progress is stalling because health systems have not evolved to meet the challenge of identifying and managing high-risk pregnancies and efficiently responding to rapid clinical deterioration. Middle SDI geographies have historically had a higher proportion of cases due to conditions such as hypertensive disorders of pregnancy and other direct maternal disorders (e.g. cardiomyopathy and embolism). Maternal haemorrhage also evolves with increasing SDI because, as increased IFD and SBA lead to near universal active management of the third stage of labor, an increasing proportion of remaining haemorrhage cases—especially those that result in death—will be due to intractable uterine atony or placental disorders, both of which require high levels of performance and responsiveness from horizontally-integrated health systems[39]. This treatise is supported by the observation that many of the geographies that improved more rapidly than would have been expected after 2000 were also the biggest recipients of Development Assistance for Health (DAH),[40] funds that are often directed toward strengthening health systems, while many of those that have improved more slowly than expected have suffered from epidemics, natural disasters, and armed conflicts that impair the function of health systems and the

willingness or ability of women to seek care. Third, within any given geography, heterogeneous or slower-than-expected MMR improvements may be related to uneven ramp-up of coverage for specific modes of reproductive health care – antenatal care (ANC), in-facility delivery (IFD), skilled birth attendance (SBA), family planning services, emergency obstetric care (EmOC), and post-natal care – that are all known to decrease the risk of bad pregnancy outcomes[41,42]. Indeed, increasing utilization of reproductive health services was one of the driving factors behind establishment of the Janani Suraksha Yojana (JSY) conditional cash transfer program in India. JSY has been quite successful at increasing reproductive health care services, but even despite its popularity this program has not been as effective at reaching poor rural women, the sociodemographic group that is already at highest risk of adverse pregnancy outcomes[43]. In addition to the JSY program in India, other countries such as Nepal, Mexico, El Salvador, Honduras, Guatemala, Uruguay, and Brazil have also had success in encouraging use of reproductive care services[44,45], so this may be a viable option for countries seeking to increase women's utilisation of reproductive health care services. Fourth, the highest SDI geographies are likely also experiencing a confluence of factors leading to higher-risk pregnancies and subsequently higher-than-expected MMR, namely delay of fertility to older ages and a corresponding increase in the proportion of pregnant women with non-communicable diseases (NCDs). Other direct maternal disorders is the dominant cause of maternal death in high SDI locations, driven by cardiomyopathy and obstetric embolism, both of which are of higher risk in older women and those with preexisting conditions such as hypertension, obesity, and diabetes[46,47]. If the trend of increasing NCDs continues and, barring any breakthrough in preventing such complications, we may reasonably expect to see MMR increases begin to emerge in other geographies besides those in the highest SDI.

Because of the importance of reproductive care coverage in overall reproductive health, and to help guide specific coverage targets for achieving SDG 3.1 and 3.7, comparable metrics and monitoring on coverage of all of these reproductive health services should be integrated into regular progress reports at the global, regional, national, and subnational levels, including the development of comprehensive strategies to reach those targets. Our analysis found that an MMR of 70 is expected with an SDI level of 0.65, which corresponds to average income of $2,648 per capita, a TFR of 2.0, and completing 12 years of education, so even lower income countries may have a path to SDG 3.1 attainment. An MMR of 70 is also associated with approximately 91% coverage of one ANC visit, 78% of four ANC visits, 81% of IFD, and 87% of SBA. Higher MMR locations have historically had much lower coverage of these services, particularly IFD and SBA, and increasing access to them will require sustained focus.

Quality of care must also be a focus as coverage of family planning services, ANC, IFD, SBA, EmOC, and post-natal care increase, because the existence of these programs by themselves is not sufficient to ensure that women are receiving the care they need during pregnancy and the post-partum period[48]. Care should be integrated and not be focused on single vertical interventions[49]. Family planning services should be longitudinal and include provision of comprehensive sex education, multiple modes of modern contraception, and access to safe abortion[50]. High-quality ANC should reflect appropriate utilization of services, good communication between patient and provider, and reliable screening and treatment for infectious diseases, (e.g., sexually transmitted infections), chronic conditions (e.g., blood disorders, obesity, substance abuse, renal dysfunction, rheumatic or other heart disease) and pregnancy abnormalities (e.g., anemia, nutritional deficiencies, blood pressure, glucose, urine protein, fetal growth anomalies)[51,52]. IFD and SBA services must be adequately staffed to meet demand and, because not all major complications of pregnancy are avoidable or easily predictable, women need to have ready access

to well-functioning basic and comprehensive emergency obstetric care (EmOC) services. These services must be appropriately distributed to meet demand[53] and be staffed by sufficient numbers of trained midwives, nurses, anesthesia and obstetrical providers to meet demand, including on nights and weekends. Health professionals in EmOC facilities also need to have appropriate equipment including medications, access to blood transfusion materials, and intensive care services to help prevent complications from leading to death[54,55]. Post-natal care should focus on detection and treatment of those conditions known to be more common in the postpartum and late maternal period, including cardiomyopathy, pulmonary embolism, and renal complications[56,57]. In countries with generalized HIV epidemics, AIDS-related deaths have also been observed to commonly occur 42 days or more after pregnancy ends, and care efforts for HIV-positive mothers should focus on ensuring uninterrupted antiretroviral treatment[58,59].

Late maternal death statistics need to be improved. Maternal mortality surveillance studies such as confidential enquiry (CE) have revealed that late maternal death is non-trivial in even low-resource settings[35,60] and may account for up to 40% of maternal deaths in high-income settings[61]. A contemporary linkage study in Mexico found that 18% of maternal deaths are missed when the definition is truncated at 42 days postpartum[62]. As immediate mortality continues to decrease as a result of improved antenatal, obstetric, and postpartum care, it is therefore increasingly likely that the proportion of late maternal deaths will continue to increase. Despite knowledge of its importance, only a minority of countries using ICD-10 reliably code late maternal deaths. This is especially egregious as many of the same countries who have completed multiple CEs also have not recorded a single late maternal death in their official statistics. Denmark, Ireland, Finland, and the United Kingdom all fall into this category. Australia, France, and South Africa likewise completed multiple CEs and have recorded a total of eight maternal deaths combined in the entirety of their official statistics. This is the exact inverse of the United States where no nationally comprehensive CEs have been completed (although some states have established maternal mortality review boards). The US has high MMR for a high-SDI country—and is one of the few where it is increasing – but following the lead of Mexico and much of Latin America, it is also one of the only countries that has proactively improved its civil registration system with addition of a pregnancy checkbox on the standard death certificate[63], so it is possible that at least a portion of the increase is related to enhanced case ascertainment[63]. The US should learn from the experiences of other countries and consider implementing regular, comprehensive CEs into drivers of maternal mortality. Other countries and subnational locations should follow the lead of the countries of the Americas by adding pregnancy checkboxes to their official death certificates and also ensuring that cooperation between their national statistics office and CE committees maximizes data quality.

Comparison to WHO maternal mortality estimates

The WHO also recently published a set of maternal mortality estimates for 1990 to 2015[64,65] as part of its collaboration with the UN Maternal Mortality Estimation Inter-Agency Group (MMEIG). MMEIG 2015 global results again show a steep decline in maternal mortality from 1995 to 2005, and some deceleration in the period 2005 to 2015 when maternal and newborn health DAH increased rapidly. GBD 2015 shows relatively little progress in the 1990s, but acceleration in MMR declines particularly after 2005. We have previously discussed some of the important differences between the analytic approaches used by GBD and MMEIG[66]. These included differences in dataset content, data processing methods, all-cause mortality, model specification, quantification of uncertainty, the use of CoDCorrect to ensure consistency between all specific causes of death, and the fact that MMEIG 2013 combined three

separate estimation methods for different categories of countries whereas GBD uses a single approach for all countries.

MMEIG has made some important modifications to their analysis since 2013, most notably implementation of a Bayesian approach that combines all countries into a single model to estimate maternal mortality cause fractions (the proportion of all deaths in the population that are due to maternal causes). These changes are especially apparent in estimates for a number of countries including South Korea, Malaysia, Sri Lanka, Kiribati, Cyprus, Finland, Georgia, Mongolia, Romania, Estonia, Latvia, Russia, and Bosnia and Herzegovina. Figures comparing MMEIG 2015 and GBD 2015 data inputs and results for each country are contained in the appendix. The correlation in MMR between MMEIG 2015 and GBD 2015 estimates is now 0.85 over the entire time period from 1990 to 2015; this compares to a correlation in MMR between GBD 2013 and MMEIG 2013 of 0.77. If we limit the comparison to 2005 to 2015, correlation in MMR increases to 0.89.

Overall drivers of differences

Figure 11 compares the country-specific trends from 1990 to 2015 between the two analyses. Whereas GBD 2015 identified only ten countries as likely having achieved MDG 5, MMEIG 2015 found a total of 18 achieved the MDG 5 target. Because both groups use the same set of live births estimates from the UN Population Division, with the exception that GBD 2015 estimated maternal mortality for the entire age range from 10 to 54 years, differences in fertility are unlikely to be a major driver of differences between the two results. Drivers of differences can thus be best summarized as being due to differences in maternal cause fraction estimates or differences in all-cause mortality numbers as shown in Figure 12.

Global MMR estimates in 1990 were much higher in the MMEIG 2015 analysis, driven largely by higher estimates of maternal cause fraction in sub-Saharan Africa, South Asia, Central Asia, central Latin America, and North Africa and the Middle East. MMEIG 2015 all-cause mortality estimates for 1990 were also higher in many of these same regions as well as in Tropical and Andean Latin America, all of which led to higher MMR estimates than those produced by GBD 2015. Of note, GBD 2015 maternal cause fraction estimates were higher in most high-income regions, central Europe, and Oceania. In contrast, our decomposition of the drivers of differences in 2015 estimates show that differences in maternal cause fraction and all-cause mortality estimates narrowed in South Asia, central Asia, and much of sub-Saharan Africa, which has on aggregate led to broad agreement in global MMR figures for 2015. GBD 2015 estimates of maternal cause fraction estimates remain notably higher in high-income North America, Western Europe, and Oceania, although it is likely that much of this is driven by MMEIG 2015 exclusion of late maternal mortality.

Comparison of data sources as a driver of divergent maternal cause-fraction estimates

As shown in Table 1, the total number of sources used by MMEIG 2015 was 203 and by GBD 2015 was 599. Appendix Table 3 shows all country-specific sources by type used in each analysis. For a number of populous countries—including China, Ethiopia, Indonesia, and India—differences in maternal cause fraction estimates are largely driven by dataset content. MMEIG 2015 did not include data from Medical Certification of Cause of Death (MCCD)[67] or the Survey of Causes of Death (SCD)[68] from India, several years of census and verbal autopsy data from Indonesia and Ethiopia, and maternal mortality surveillance data from China. MMEIG 2015 similarly did not include VR data from Iran and Dominican Republic or sibling history from Jordan, all of which led to very different estimates of levels and trends of maternal mortality in those countries. In total, 396 sources were excluded by MMEIG 2015. In many

cases the MMEIG 2015 documentation does not describe reasons for not including these data. In future iterations of both the GBD and MMEIG estimation, the groups should both work more closely to ensure relevant data sources are included in both analyses.

Comparison of data processing methods

Differences in processing methods of sibling history data are important, especially for countries in sub-Saharan Africa. The nine countries without maternal mortality data in the GBD 2015 analysis were Andorra, Angola, Equatorial Guinea, the Federated States of Micronesia, Marshall Islands, Samoa, Solomon Islands, Somalia, and Vanuatu. MMEIG 2015 had no data for 23 GBD 2015 countries or territories, including Angola, Djibouti, Federated States of Micronesia, Guinea Bissau, North Korea, Palestine, Papua New Guinea, Samoa, Solomon Islands, Somalia, Tonga, and Vanuatu. They did not generate estimates at all for American Samoa, Andorra, Antigua and Barbuda, Bermuda, Dominica, Greenland, Guam, Marshall Islands, Seychelles, Taiwan, and US Virgin Islands.

GBD 2015 utilized single-year sibling history survival data from each source, applied Gakidou-King weights to adjust for survivor bias, corrected for incidental HIV deaths using country-year-age-specific information on the PAF of HIV to maternal death, and employed Bayesian noise-reduction algorithms to help reduce stochastic variability in data. On aggregate, this approach maximizes capture of underlying information on levels and trends of pregnancy-related mortality in health surveys. MMEIG 2015 combined all data from each survey and assigned them to the midpoint year of the recall period. They then uniformly applied a correction factor to reduce every datum by 10% or 15%, depending on the geography. The resulting MMEIG dataset is relatively sparse in some locations, and estimates are driven by regression coefficients. Examples can be seen in Democratic Republic of the Congo, Saudi Arabia, Ghana, and Ethiopia (see Appendix Figure 3). We would encourage MMEIG to consider using single-year sibling history data in their future analyses, as this difference in data processing may be driving divergence in trends from the early part of the MDG period, especially in sub-Saharan Africa.

Another important dataset difference is in the method used for processing and adjustment of VR data. GBD uses a standardised approach for all causes of death, empirically analysing every location's single-year VR quality to guide dynamic adjustments to raw data (Figure 13). In past studies, MMEIG applied a default correction factor of 1.5 to all VR data. That method was modified in two ways in 2015. First, correction factors for VR were adjusted to match the deaths in published surveillance studies for those countries that had completed them. Second, MMEIG 2015 reclassified selected recent years of VR data as special studies. These reclassified years were not subjected to the 1.5 correction factor, but earlier years were. This reclassification resulted in estimates showing faster declines in the MMR than are supported by raw data. These seven countries where the MMEIG results are affected by the selective VR reclassification are Brazil, Costa Rica, Cuba, Ecuador, Guatemala, Kazakhstan, Mexico, and Uruguay. The criteria used for reclassification of VR as special studies are not clearly documented, and it is unclear if these criteria have been objectively applied to all country-years of VR.

Comparison of modeling methods

MMEIG implemented a Bayesian approach to estimating maternal mortality for the first time in their 2015 estimates, which dramatically improved their model fit in countries with long time series of data. However, the base MMEIG model still relied on a simple linear mixed-effects model with only three covariates—gross domestic product (GDP), general fertility rate (GFR), and skilled attendance at birth (SAB)—and country random effects. In contrast, the GBD 2015 used four families of statistical models

and using 15 different covariates to develop ensemble models that were chosen based on a robust out-of-sample validity testing. MMEIG models were developed for the aggregate age range of 15 to 49 years, while the GBD 2015 estimates were generated separately for nine different 5-year age bands ranging from 10 to 54 years. The latter approach has the noted advantage of being able to automatically adjust for compositional bias if the age structure of the sample population is different than the general population. It also facilitates insight into potentially divergent age trends in maternal mortality within individual populations, matching them with corresponding shifts in age-specific fertility. Such an approach is crucial to singling out, for example, the contribution of adolescent fertility to overall maternal mortality levels and trends in maternal mortality. We therefore believe age-specific maternal mortality estimates, covering the entire reproductive age range, should be standard practice.

All-cause mortality estimates

While recognizing the potential caveats of adult mortality rates estimated using sibling survival, we made important improvements in GBD 2015 in accounting for selection bias and recall bias. We incorporated the uncertainty around adult mortality rate into our all-cause mortality estimation process for countries affected by HIV/AIDS in the sub-Saharan Africa regions. We did this by using single-year data on adult mortality rate from sibling survival modules—instead of pooled data for five-year periods—and the crude death rate due to HIV/AIDS into the Space-Time Gaussian Process Regression that generates adult mortality rate estimates. This approach helped reconciliation between all-cause mortality estimates based on demographic sources and the HIV-specific mortality estimates using EPP-Spectrum, thus allowing us to better capture levels and trends of mortality in adult women, especially in western and central sub-Saharan Africa. In contrast, mortality estimates from WPP 2015 do not incorporate all available data, do not explicitly reconcile HIV-related and background mortality estimates, and for many countries are largely based on a tabular model life table system derived from that age pattern of mortality from countries in the 1950s and 1960s and a single entry parameter, the under-5 mortality rate. Such a system is likely to misrepresent the changing relationship between mortality in child age groups and adult age groups[69] and, as we see from WPP 2015 all-cause mortality estimates in the 1990s, may overestimate mortality in western and central sub-Saharan Africa[70].

Quantification of uncertainty

The GBD approach to quantification of uncertainty assumes that uncertainty is uncorrelated in all locations. MMEIG has in the past assumed uncertainty is 50% correlated and 50% uncorrelated. This has led to very large uncertainty intervals in many countries and at the global level in past reports. MMEIG 2015 has implemented a more rigorous statistical approach to estimating uncertainty but has chosen the non-standard step of reporting only 80% uncertainty intervals, despite the general global health practice of reporting 95% UIs. The rationale provided for this decision was that 95% UIs cannot be reliably interpreted, although why 80% intervals are more interpretable is unclear. In the interests of transparency and comparability to other analyses such as the GBD, we hope that in future estimates MMEIG will provide 95% uncertainty intervals along with other narrower intervals.

Limitations

This analysis, like many before it, has a number of limitations. First, despite continued increase in the size and breadth of our data sources, there are still several countries and territories from which we have no data on maternal mortality. In a number of other locations, especially low-SDI geographies, we continue to rely on data reporting aggregate pregnancy-related deaths from surveys and censuses.

Unlike VA and VR sources, survey and census data sources do not differentiate between maternal and non-maternal (incidental) deaths during pregnancy. The degree to which underreporting due to survival and recall bias offsets overreporting due to inclusion of incidental deaths is unclear and is further reason to advocate for improved data collection efforts. Second, while we report results on the entire period from 1990 to 2015, because of large lag times in release of data we have not been able to include any data from 2015 and data from only 13 countries from 2014. Final 2015 results are thus based on recent historical data and model results. Third, our CODEm models have limited ability to capture non-stochastic rapid increases and decreases that may occur as a result of epidemics such as Ebola and H1N1 influenza[71,72], armed conflicts[73], or other events. Fourth, this report has examined nine specific etiologic categories of maternal death, but this classification system is certainly not exhaustive. We have not evaluated the contributions of some important chronic conditions known to increase risk to pregnant women such as obesity, diabetes, heart disease, hemoglobinopathies such as sickle cell disease, chronic kidney disease, and chronic hypertension, or specific risk factors that may contribute to mortality. Our evaluation of ectopic pregnancy, abortion, and miscarriage together limits the ability to specifically quantify the burden of unsafe abortion. We likewise have not disaggregated the other direct obstetric complications category to quantify the relative importance of anesthesia complications, cardiomyopathy, and pulmonary embolism, all of which are known to be important contributors to maternal mortality in many settings. Continuing to improve on the specificity of our analysis of the underlying etiology of maternal death will be expected to improve the clinical utility of GBD estimates. Fifth, while the GBD approach has the ability to provide excellent detail on geographic and temporal trends in maternal mortality, it has limited ability to explore subpopulations which are not geographically based, including indigenous populations or other high-risk groups who may have higher MMR due to cultural, religious, or other differences.

Conclusions

A shift from a relative target of percent reduction in MDGs to an absolute threshold target of an MMR of 70 in the SDGs has important ramifications. It will emphasise countries with high maternal mortality rates over those that have already achieved the goal. Such emphasis may be beneficial in that it should help focus additional international attention and resources on those countries who have the farthest distance to go. On the other hand, preemptive "achievement" of SDG 3.1 has the potential to sap political and financial investment in reproductive health in countries that still have significant numbers of preventable maternal deaths, especially when continued progress is likely to depend largely on improvements in overall health systems performance[74–78]. One approach to mitigate this risk would be to promote SDG 3.1 not only as a threshold goal for nations on aggregate, but also a target for all sub-populations within each. This will require all stakeholders to make disaggregated data and information on women's, children's and adolescents' health publicly available[5]. Furthermore, as the global community pursues SDG 3.1, it will be important to monitor and report on all aspects of reproductive health care as outlined in SDG 3.7[5]. This will require the international community to pay heed to the intricately related issues of immigration, armed conflicts, epidemics and pandemics, environment, economic instability, and gender equality, all of which can have significant effects on availability and quality of reproductive health services and women's willingness to seek them.

Global progress in reducing maternal mortality has been accelerating in the past 15 years, but there is still significant work left to do. More than 250,000 women died during or following pregnancy in 2015, the vast majority of which were preventable deaths. Each woman that died left children, widowers,

family, and their communities behind. The quantitative effect of MDG 5 is difficult to measure, but it is even harder to dispute the notion that it has united the international community in striving to decrease maternal mortality. With the ratification of SDG 3.1 and SDG 3.7, relevant stakeholders need to make informed decisions about how to prioritise actions needed to bring about continued progress, and they can only do that with better data. As we continue on the path toward 2030, necessary and urgent steps will include rapid improvement in cause of death data collection systems and data dissemination coupled with more effective and widespread action and policies to promote education of girls and women, provide them comprehensive family planning services, and ensure that each and every woman has access to the types of reproductive care they need to survive – and thrive.

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Figures and Tables