CONFIDENTIAL – DO NOT CIRCULATE

Global, regional, and national levels of age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013

GBD Mortality and Causes of Death Collaborators

Abstract

Background

Up to date evidence on levels and trends in age-sex specific all-cause and cause-specific mortality is an essential input into debates on global, regional, and national health policies. In the Global Burden of Disease Study 2013 (GBD 2013) we aimed to estimate annual deaths for 188 countries between 1990 and 2013. We used the results to examine if there is epidemiological convergence across countries.

Methods

We estimated age-sex specific all-cause mortality using the GBD 2010 methods with some refinements to improve accuracy applied to an updated database of vital registration, survey, and census data. Our approach to cause of death estimation generally followed GBD 2010 methods. Key improvements included a major expansion of data available through the addition of more recent vital registration data for 72 countries, an updated verbal autopsy literature review, two new and highly detailed data systems for China and noteworthy expansions of detail for Mexico, the United Kingdom, Turkey, and Russia. Statistical models for garbage code redistribution were improved for several major garbage codes. Six different modeling strategies were used across the 240 causes; cause of death ensemble modeling (CODEm) was the dominant strategy for causes with sufficiently rich information. Time trends for Alzheimer's disease and other dementias were informed by meta-regression of prevalence studies. For pathogen-specific etiologies of diarrhoea and lower respiratory infections we shifted to using a counterfactual approach. We computed two types of metrics of convergence (inequality) across countries: the average relative difference across all pairs of countries (Gini coefficient) and the average absolute difference across countries. To summarize broad findings, we used multiple decrement life tables to decompose probabilities of death from birth to exact age 15, from exact age 15 to exact age 50, from exact age 50 to exact age 75, and life expectancy at birth into major causes. For all quantities reported, we computed 95% uncertainty intervals. We constrained cause-specific fractions within each age-sex-country-year group to sum to all-cause mortality based on draws from the uncertainty distributions.

Results

Global life expectancy for both sexes increased from 65.3 in 1990 to 71.5 in 2013 while the number of deaths increased from 47.5 million to 54.9 million over the same interval. Global progress marked variation by age and sex: declines in children have been the largest with average absolute differences between countries decreasing but relative differences measured by the Gini coefficient increasing. For women 25-39 years and over 75 and for men 20-49 years and 65 and over both absolute and relative differences are increasing. Decomposition of global and regional life expectancy shows the prominent

role of reductions in age-standardized rates due to cardiovascular diseases and cancers in developed regions, and reductions in child deaths from diarrhea, lower respiratory infections and neonatal causes in developing regions. HIV/AIDS led to large decreases over the period in life expectancy in southern sub-Saharan Africa. For most communicable causes of death both death numbers and age-standardized rates have been declining while for most non-communicable causes due to demographic shifts death numbers have increased but age-standardized rates have declined. For a small number of causes which cause over 100 thousand deaths a year in 2013, age-standardized rates increased between 1990 and 2013 including HIV/AIDS, pancreatic cancer, atrial fibrillation and flutter, drug use disorders, diabetes, chronic kidney disease, and sickle cell anemias. Analysis of the leading causes of deaths under age 5 highlights the continued role of diarrheal diseases, lower respiratory infections, neonatal causes, and malaria. The most important pathogens are rotavirus for diarrhea and pneumococcus for lower respiratory infections. Analysis of country-specific probabilities of death over three phases of the life cycle reveal marked variation between and within regions.

Interpretation

For most countries, the general pattern of reductions in age-sex specific mortality has been associated with a progressive shift towards a larger share of the remaining deaths due to NCDs and injuries. Judgments on whether there is epidemiological convergence across countries depend critically on whether an absolute or relative metric of inequality is used. Age-standardized rates for seven substantial causes are, nevertheless, increasing pointing to the potential for reversals in some countries. Important gaps exist in the empirical data for cause of death estimation for some countries; for example, no national data for India is available in the last decade. The annual GBD summarizes the evidence on mortality and causes of death for each country and the limitations of existing data.

Funding

Bill & Melinda Gates Foundation

Introduction

The Global Burden of Disease (GBD) study provides a unique comprehensive framework to systematically assess national trends in age- and sex-specific all-cause and cause-specific mortality. Recent and comprehensive evidence on levels and trends for each country is a critical input to more informed priority setting. Trends provide an opportunity to quantify progress against explicit health targets whether local, national, or global and to evaluate where programs are working or not. Quantification across populations and over time using comparable definitions and methods can also facilitate meaningful benchmarking efforts. Regular comprehensive cause of death updates will identify emerging public health challenges. The Global Burden of Disease 2013 study provides the first evidence (or output) from the shift to a continuously updated approach to global health surveillance.[1]

The GBD 2010 study, a collaboration of 488 investigators, highlighted critical global and regional trends in all-cause and cause-specific mortality.[2–8] The GBD 2010 reported substantial declines in child mortality driven by reductions in diarrhoea, lower respiratory infections, and more recently, malaria. The lowest income regions documented progress in combating maternal mortality, HIV/AIDS, tuberculosis, and malaria. Nevertheless, a substantial unfinished agenda remains for these Millennium

Development Goal-related diseases. Outside of sub-Saharan Africa, the period 1990 to 2010 was associated with rapid shifts towards a larger share of death from non-communicable diseases and injuries and a rising mean age of death. Country analyses using the GBD 2010 database have been reported for China, the United Kingdom, Mexico, Iran, and the United States taking advantage of the comparable methods and definitions of the GBD to benchmark these countries against a variety of peers.[9–16]

Substantial debate surrounds what should follow the Millennium Development Goals, objective, timely, and comprehensive evidence on the levels and trends in causes of death can be a useful input. Ambitious goals have been discussed[16] such as the elimination of preventable child and maternal mortality in a generation. Targets of "zero disease" have been formulated for HIV/AIDS, tuberculosis, and malaria by various groups.[17–23] The Lancet Commission on Investing in Health argued that the world can achieve a Grand Convergence between poor and rich country health by 2035. Advocates for non-communicable disease programs argue that rapid epidemiological transitions in many regions of the world require broader health goals for the development community. Movements to place universal health coverage at the center of the post-2015 health agenda are highlighting the consequences of failure to meet basic health care needs. [24–27] Up to date evidence on levels, trends, and inequality in mortality and causes of death can inform these critical global discussions.

Broad interest in the GBD 2010 has led to the expansion of the GBD collaboration to include more than 1000 investigators in 106 countries. The GBD 2013 not only incorporates newly published or released datasets particularly over the last five years but also expands the analysis in some important directions. Sub-national assessments have been incorporated for provinces of China, states of Mexico, and regions of the United Kingdom. These subnational assessments enhance the value to national decision-makers of the results by identifying inequalities and the local variation in the leading diseases, injuries, and risk factors. The cause list has been expanded and through the collaborations of the GBD 2013 many new and more detailed data sources incorporated. We report on the new findings for the first time at the country-level for the period 1990 to 2013. Country level results by cause allow a careful assessment of where and for which diseases and injuries the risk of death worldwide is converging or diverging. This work provides essential intelligence for influential groups calling for a grand convergence in global health.

Methods

The GBD approach to estimating all-cause mortality and cause-specific mortality has been previously described.[2,3] Here we describe several methodological refinements.[28] Figure 1 outlines the general approach to all-cause mortality and cause-specific mortality analysis and their interactions. Given 240 causes, the overall schematic is a simplification but provides a high-level general assessment of all the analytical steps involved in estimating mortality and causes of death. The GBD 2010 cause list included 291 causes of death or disability of which 235 are causes of death; we have expanded the cause list to include 303 causes of which 240 are causes of death. The extra causes were added based on three considerations: a) causes which were for epidemiological reasons already modeled separately but reported combined with other causes in GBD 2010, such as for example, silicosis, asbestosis, anorexia nervosa, and typhoid and paratyphoid fever; b) the category of other unintentional injuries was large and heterogeneous so it was broken down further to include pulmonary aspiration and foreign body in trachea or lung, foreign body in other part of body, and unintentional suffocation; and c) new datasets

became available to allow estimation of mesothelioma, new maternal sub-causes, neonatal hemolytic anemia, and chronic kidney disease due to glomerulonephritis. Appendix table 14 (pp 245-251) provides the ICD codes for the GBD 2013 cause list. Based on broad consultation, we have removed from the cause list the pathogen-specific etiologies for diarrhoeal diseases and lower respiratory infections. Instead, we analyze these etiologies using a counterfactual approach -- see below for more detail.

We use the division of the countries of the world into 21 regions and seven super-regions as defined in the GBD 2010. The GBD 2013 also includes an assessment of subnational populations in three countries: provinces for China, states for Mexico, and the United Kingdom broken down into Scotland, Wales, Northern Ireland, and nine regions of England. These countries have been analyzed at the sub-national level because of the interest of national collaborators and because sufficient data were made available by teams in each country. In future iterations of the GBD, we hope to include further subnational breakdowns. In addition, for purposes of improving estimation of mortality and causes of death, data sources for India have been separately analyzed for rural and urban areas. This facilitated the analysis of many cause of death sources which were specific to urban or rural areas alone.

Covariates

National-level time series (from 1980 to 2013) for a wide range of covariates were estimated based on data from available survey microdata, censuses, official reports, administrative data, as well as systematic literature review. For lagged distributed income and education, national-level time series were estimated from 1950 to 2013. Detailed publications on the data and methods used to generate the imputed series for GDP, educational attainment, tobacco prevalence and obesity prevalence have been published.[29–32] Table 1 provides the source and imputation method used to generate a complete time-series for each covariate. In general, uncertainty in covariates values have been estimated for some covariates where sufficient information is available.

All-cause mortality

A new analysis of available data on levels of all-cause mortality for 188 countries has been undertaken from 1950 to 2013; we present only results for 1990 to 2013 in this paper to coincide with the period of the overall GBD 2013 assessment. The number of countries compared to the GBD 2010 has increased by one to reflect the split of South Sudan; within the GBD 2013 data was re-extracted and new estimates were separately generated for Sudan and South Sudan. In terms of methodology, improvements have been made in data source bias adjustment for child mortality analysis, utilizing the improved functional forms between summary mortality indicators in child (under age five) and adult (age 15-59) age groups and other covariates including crude death rates due to HIV/AIDS, and a modification of the model life table system to use a unified standard life table selection process and improved re-distribution of excess mortality rate from HIV/AIDS. We divide the analysis into eight steps and provide a brief overview. Input data and key indicators for all countries can be viewed in the online data visualization for all-cause mortality [*will insert URL when active*].

1) Estimation of under-five mortality ($_5q_0$)

All survey, census, sample registration, and vital registration sources have been analyzed. Wherever possible, the microdata from surveys and censuses have been analyzed using updated methods for child mortality.[33] All measurements of under-five mortality have been synthesized using Spatio-temporal

regression and Gaussian Process Regression (GPR). Wang et al[33] provides substantial detail on this analysis for the GBD 2013. The GBD 2013 analysis included correction for bias in different sources in specific countries.

2) Estimation of adult mortality (${}_{45}q_{15}$)

Following the GBD 2010 methods, we systematically identified all available vital registration data, sibling history survey data, sample registration data, and household recall of deaths. Vital registration data were evaluated for completeness using optimized death distribution methods.[2,34] Sibling history data were analyzed to account for survivor bias, zero-surviving sibships, and recall bias.[2,35] All sources are synthesized using the combination of spatio-temporal regression and GPR. The mean function for the GPR is based on the combination of a non-linear hierarchical model with income per capita, mean years of education in age group 15 to 60, mortality rate due to HIV/AIDS, and country random effects[2] as covariates, and a spatio-temporal regression where we add to the first stage model without country random effects the smoothed residuals between the first stage model and observed data (see appendix pp 66-79 for more detail). The hyper-parameters used in GPR are selected through an out-of-sample predictive validity testing process as described in Wang et al.[2] We rake the estimated sub-national adult mortality in China, India, Mexico, and the UK to ensure that the sum of sub-national estimates for a given age-sex group equal the national estimates accounting for differential population size.

3) HIV-free under-five mortality and adult mortality

HIV/AIDS causes more excess mortality in younger ages and thus changes the age pattern of mortality which otherwise can be readily described by Gompertz law of mortality or the Kannisto-Thatcher model.[36,37] Where HIV/AIDS is common, this pattern of mortality must be explicitly taken into account. As a first step, we estimate the HIV-counterfactual under-five mortality and adult mortality rates by using the non-linear mixed effects model from the previous step and setting the crude death rates due to HIV/AIDS in the respective age groups to zero (see appendix pp 90-94 for more detail).

4) HIV-free life table

The GBD 2010 introduced a model life table system that uses the under-five death rate (${}_5q_0$) and adult mortality rate (${}_{45}q_{15}$) along with a selected standard mortality schedule to estimate the full age pattern of mortality for country-years of interests.[33] For GBD 2013, we have modified how the standard mortality schedule is selected for each country-year so that the same approach is used for all countries. Specifically, we compute empirically a set of space-time weights that relate the observed age pattern of the probability of death in a sex-country-year with other sex-country-year observations. These weights have been derived by comparing every empirical life table that is not affected by HIV/AIDS epidemic in the GBD database (10,673 life tables) with every other life table of the same sex. We estimated space-time weights as a function of the time lag between the paired life tables and location (i.e., within the country, GBD Region, or GBD super region). These weights were estimated as the inverse of the average sum of age-specific differences in the logit of the probability of death (see appendix pp 79-91 for more detail). The key observation from this spatial-temporal analysis of age-specific probabilities of death is that the mortality pattern in a country in a given year is more strongly related to the mortality pattern in the same country within 15 years than to mortality patterns in other countries; however, other countries in the same region or other regions generally are similarly related when the lag in time is over 20 years.

5) Age-Pattern of HIV/AIDS mortality

Excess mortality from HIV/AIDS as quantified between the estimated ${}_5q_0$ and ${}_{45}q_{15}$ with their HIV-counterfactual counterparts leads to increased mortality in specific age groups. This excess HIV/AIDS mortality is assigned by age using the estimated relative risk of death due to HIV/AIDS in an age-group compared to the HIV/AIDS excess death rate in age-group 40-44. These relative risks are estimated using data from vital registration systems that have ICD10 coded causes of death from HIV/AIDS which includes South Africa.[38] We used Seemingly Unrelated Regression (SUR) model[39] with only a constant and generated 95% uncertainty intervals for the age pattern of relative risks by repeatedly sampling from the mean and covariance matrix of the estimated betas and the error term. SUR allows the error term of a series of linear regressions to be correlated. We use separate regressions by sex and for the pattern of mortality in concentrated epidemics and generalized epidemics as defined by UNAIDS.[38–40]

6) Minimizing the difference between demographic estimation of age-specific mortality and HIV models

Murray et al.[38] use a refined version of the EPP-Spectrum framework to model HIV/AIDS mortality. This analysis yields very large uncertainty intervals for HIV/AIDS in many countries. However, in some Southern African countries, there remains a marked discrepancy between data on all-cause mortality and estimates of HIV/AIDS mortality with demographic sources suggesting smaller epidemics. To minimize the difference between HIV/AIDS mortality and the demographic estimates that are also uncertain, we compute a loss function which quantifies the extent to which the age-sex-country-year HIV/AIDS estimates exceed all-cause mortality:

$$e_r = \sum_t \sum_a \sum_s \max(0, m^{HIV}_{r,t,a,s} - .8 * m^{all-cause}_{r,t,a,s})$$

For run *r* of a given country, excess mortality, *e*, is equal to the sum of all non-zero differences between HIV/AIDS mortality, m^{HIV}, and 0.8 times a randomly selected all-cause mortality draw, $m^{all\text{-}cause}$, across all year-age-sex combinations (*t*, *a*, and *s* respectively). The number 0.8 is the highest observed cause fraction due to HIV in any age-group in any vital registration system. We select from the uncertainty ranges for HIV and all-cause mortality those that minimize the difference. If there are no draws for which the loss function is positive, we sample randomly from all matched draws.

HIV/AIDS cause-specific mortality is included in the CoDCorrect algorithm. The CoDCorrect algorithm (see below) can alter the age and time distribution of deaths from HIV/AIDS. In order to incorporate the overall change in the volume of HIV/AIDS deaths over the course of the epidemic in a country implied by the application of the CoDCorrect algorithm, but not to distort the Spectrum estimated time and age pattern, we adjust the entire HIV/AIDS epidemic up or down based on the cumulative effects of CoDCorrect on HIV/AIDS through 2013 in a country.

7) Mortality shocks: natural disaster and armed conflict

We follow the same methodology used by Wang et al. 2012[2] to generate child mortality rate and adult mortality rate under the influence of natural disasters and armed conflicts. Conflict and war data, including deaths from one-sided violence, non-state conflict, armed force battles, and other inter- or intra-state conflicts, are obtained from the Uppsala Conflict Data Program[41] and the International Institute for Strategic Studies.[42] Further war data is obtained from countries' vital registration systems and is classified as due to war.[43] We include disaster data in the International Disaster Database from

the Center for Research on the Epidemiology of Disasters.[44] From this database, we include deaths due to complex disaster, drought, earthquake, flood, etc. When these databases are not fully up-to-date or do not contain shocks documented to exist, we supplement with case-by-case sources. These with-shock mortality rates are then used as entry parameters to the GBD relational model life table system to generate age-specific mortality rates with the impact of shocks added.

8) Estimated numbers of deaths by age and sex

Age and sex-specific death rates from the life table are used to generate death numbers by multiplying by population estimates from the World Population Prospects 2012 revision and the Human Mortality Database for age groups higher than age five.[45] For the under-five age groups, we apply the method developed by Wang et al 2012. In some cases, GBD collaborators have pointed out that assumptions in the UN estimation process have led to implausible population numbers for selected country and age-groups. A case in point is the low population estimates for older age groups in South Africa especially for the most recent years. For GBD 2013, we have applied a recently developed Bayesian population reconstruction model by Wheldon et al 2003[46] to re-estimate population for South Africa for the time period 1970 -2013.

Cause of death database development

Lozano et al.[3] described in detail the key steps in the development of the GBD cause of death database. The database has been expanded to capture 2233 additional site-years of vital registration data and 52 additional verbal autopsy site-years; a site-year is defined as data for a specific geographical location in a given year such as a province of China. Table 2 summarizes the number of studies and number of additional studies since GBD 2010. A major new addition has been the incorporation of two data systems in China. First, the China National Office for Maternal and Child Health Surveillance provided detailed information on child and maternal mortality by cause from 363 surveillance sites, as of 2013, in China for years 1996-2013. Second, the National Vital Statistics Information Center at the Chinese Center for Disease Control and Prevention collected and provided the cause of death information for years 2004-2012, which included 4.0 million deaths in 2012. In addition, China Disease Surveillance Points (DSP) data for the period 1991-2003 disaggregated for the same strata have been incorporated in the analysis. Data have been disaggregated for both systems by province and urban and rural strata within province. New datasets have been obtained for Russia that provide more detailed causes (see appendix pp 180-244 for more detail). Turkey expanded the coverage of their vital registration system to cover nearly all of the population after 2009 and this new data has been incorporated into the analysis. In total we identified 538 verbal autopsy (VA) site-years, 52 more than in GBD 2010. Countries with the most VA site-years available include India, Bangladesh, and Tanzania. Data from all VA studies was re-extracted and re-mapped to ensure consistency with the GBD 2013 cause list. We excluded from the database verbal autopsy studies reporting cause assignment using InterVA because of extremely low published validity for InterVA.[47] We have incorporated a total of 1145 registry-years of new cancer data, including 128 from the recently released Cancer Incidence in Five Continents Volume X[48] and 1017 from supplemental sources. Our analytical approach for using cancer incidence data and models of the death to incidence ratio remains unchanged from GBD 2010. Figure 2 shows site-years of data by country for any cause. Of note, Somalia and Equatorial New Guinea have no cause of death data for any specific cause.

Assessment and enhancement of cause of death data quality and comparability

Using the general approach of the GBD 2010, we followed six steps to assess the quality of the data and enhance comparability. First, we adjust cause of death data from vital registration systems for incompleteness. The analysis of all-cause mortality described above yields a separate estimate of completeness for deaths under age five and deaths over age five which we use to correct the cause of death data. When correcting for incomplete registration we make the strong assumption that for a given age-sex-country group the cause of death composition of registered deaths and non-registered deaths are the same. 77% of data points were from registration or sample registration that were more than 85% complete, 17% from systems that were 70-84% complete and 6% less than 70% complete. Of the 6% of observations less than 70% complete, most (62%) of these observations were in children under age five. In the GBD 2010, we conducted sensitivity testing of excluding data below a fixed threshold of completeness for child causes of death and found that this did not substantially change the results; for this reason we have used all the data in our analysis for GBD 2013.[3]

Second, we developed 103 unique maps (excluding verbal autopsy studies) to translate causes found in the data to the GBD 2013 cause list. The expanded cause list of this study required us to adjust the maps used for data included in GBD 2010. GBD 2013 cause maps for ICD-9 and ICD-10 are given in appendix table 14 (pp 245-251). The appendix includes more detail on changes made to the handling of various shorter tabulation lists used by some countries for reporting such as the ICD-9 Basic Tabulation List (pp 252-253).

Third, a critical aspect of enhancing the comparability of cause of death data is to deal with uninformative or 'garbage' codes. Garbage codes are codes where deaths are assigned that cannot or should not be considered as the underlying cause of death. Examples include heart failure, ill-defined cancer site, senility, ill-defined external causes of injuries, and septicaemia. GBD 2010 introduced a much more detailed approach to the redistribution of garbage codes than previously attempted in prior GBD studies. Figure 3 shows the number of deaths in the database for each calendar year with the number assigned to garbage codes shown in green. Due to lags in national reporting of cause of death data, the number of deaths available after 2010 declines. Important changes for the GBD 2013 in our approach to redistributing garbage codes include the statistical estimation of the fraction of deaths following the methods outlined by Ahern et al[49] for deaths assigned to ill-defined cancer site, ill-defined external causes of injuries, heart failure, unspecified stroke, hypertension, and atherosclerosis by region, age and sex. Due to known variation in the coding of ICD-10 code X59 (Exposure to unspecified factor)[50] and its sub-causes in high-income countries, we have redistributed these garbage code using country-specific estimations for high-income countries derived from our statistical analysis. In addition, based on critical comments in the literature, we do not use malaria as a target for any garbage code redistribution in adults.[51] We have also implemented geographic restrictions on garbage code redistribution for Chagas disease based on known endemicity so that Chagas will not receive deaths in countries outside of Latin America.

Fourth, for a limited number of datasets, particularly some verbal autopsy studies, deaths are reported for broad age-groupings and/or with both sexes combined. With the addition of new data for GBD 2013 we identified 30 new age formats, totaling 112 unique age tabulations in the database. We use the algorithms described in the GBD 2010 to split these aggregated categories into estimates for specific age-sex groups.

Fifth, due to small numbers of overall deaths included in a verbal autopsy study or observed in small countries, the number of deaths by cause can fluctuate substantially from year to year. For example, in Iceland, no maternal deaths were observed from 1991 to 2000, then one maternal death in 2001. We modified our approach to smoothing these stochastic fluctuations used in the GBD 2010 by using a simple Bayesian algorithm. We assume a normally distributed prior and a normal data likelihood such that:

$$\text{Posterior Mean} = \left(\frac{\tau^2}{\tau^2+\sigma^2}X + \frac{\sigma^2}{\tau^2+\sigma^2}\mu\right)$$

$$\text{Posterior Variance} = \left(\frac{\tau^2\sigma^2}{\tau^2+\sigma^2}\right)$$

Where *X* is the mean of the data and μ is the mean of the prior. We estimated the prior for vital registration series using a negative binomial regression with fixed effects on year and age estimated separately for each country. Where the data are based on a large sample size the variance of the data is small and the prior has effectively no influence on the posterior. Where the data have a large variance due to small sample size the prior has more influence effectively borrowing strength on the age pattern from data within the same country but allowing for different levels in each year. For verbal autopsy studies, we modified this approach because many published reports are for a single site in a single year. The prior for each cause was based on a negative binomial with fixed effects for age-groups and random effects for study-year; the regression was estimated independently for each region. For malaria, studies were not grouped by region but by super-region and level of endemicity. To avoid very large negative values for log death rates or logit cause fractions, we limited the minimum non-zero posterior value to 1 per 10,000,000.

Sixth, GBD collaborators and analysts still identified 0.89% of the database entries as outliers which were excluded from the analysis. Outliers were identified based on the following four criteria. First, studies with biologically implausible values such as 100% of mortality from a single relatively rare cause. Second, studies with results that were dramatically inconsistent with other studies for the same country. Third, studies that were dramatically inconsistent with studies in other countries with similar socio-demographic profiles within the same region. Fourth, studies that if included lead to abrupt changes in model estimated time trends that could not be explained by known contextual changes or policy initiatives. Data points that were outliered are visible in the online data visualization of the cause of death database for inspection at [*will insert URL when active*].

Modelling of individual causes of death

As in the GBD 2010, we use six different modeling strategies for causes of death depending on the strength of the available data. Where extensive data are available, we used cause of death ensemble modeling (CODEm), where more limited data are available we used simpler statistical models and where available cause of death data may be substantially biased or not available we used natural history models. Appendix table 19 (pp 278-282) summarizes the modeling approach for each cause. We generate 95% uncertainty intervals from all the different modeling strategies. Uncertainty in the number of deaths for an age-sex-country-year is propagated into the computation of years of life lost for the same category.

Cause of death ensemble modeling (CODEm)

We used CODEm for 155 causes. CODEm has been extensively used in global health estimation including the GBD 2010.[3,52,53] The advantage is that a wide range of different models are tested. Only models meeting predetermined criteria in terms of the statistical significance and direction of regression coefficients are retained. 30% of the data are held out of the initial analysis so that the performance of different models is assessed in terms of how well they predict the data held out. Through multiple iterations of the hold-out process (cross-validation), stable objective information on model performance is obtained. The best performing models in terms of root-mean squared error for level and trend are combined into a model ensemble. In the case of some causes, we developed separate ensemble models for GBD developed country regions and developing regions; the main advantage of this is that uncertainty in model estimation from more heterogeneous data in developing regions does not inflate the uncertainty interval for developed countries. We have taken this approach for all cancers and transport injuries.

Negative binomial models

For 13 causes, the number of deaths in the cause of death database was too low to generate stable estimates of out-of-sample predictive validity required for CODEm. For these causes, we developed negative binomial regressions using either a constant or constant times the mean assumption for the dispersion parameter using reverse step-wise model building practice. We selected between the two model dispersion assumptions based on best fit to the data. Compared to the GBD 2010, we modified how we generated uncertainty from these regressions by including in the uncertainty sampling draws from the gamma distribution with shape equal to the expected rate (mu) / expected dispersion, and scale equal to the expected dispersion if the dispersion was assumed to be constant. For models where dispersion was assumed to equal a constant times the mean, the scale parameter included mu as a multiplicative term (instead of the shape parameter).

Data proportion models

Following the same approach as the GBD 2010, for 14 causes where death is a rare event, we first modeled the parent cause in the GBD hierarchy using CODEm and then allocated deaths to specific causes using proportions of the parent cause for each sub-cause. For these causes, no significant predictors could be identified in negative binomial regressions. We estimated proportions using simple averaging based on available vital registration data. Depending on the availability of data, we averaged the data across age, sex, region and year.

DisMod-MR models

We use DisMod-MR to estimate detailed cause fractions for several causes of death where there was sufficient data to estimate proportions of a parent cause due to sub-causes that vary across regions and countries but insufficient data to run CODEm. DisMod-MR is extensively described in Flaxman et al. 2014.[54] The source code for estimation is available at [*will provide link when active*]. DisMod-MR uses data on sub-cause fractions gathered during systematic review and from ICD-coded vital registration and sample registration systems. It utilizes two types of fixed effects (study characteristics and country covariates) with hierarchical random effects for super-region, region and country to generate estimates for each country, age-group, both sexes and six discrete time points: 1990, 1995, 2000, 2005, 2010, and 2013. Predictions for intervening years—and back to 1980—are calculated assuming an exponential

rate-of-change. We use this approach for eight causes of maternal death, four causes of meningitis, one cause of chronic kidney disease, four causes of cirrhosis, four causes of liver cancer, and three causes of hemoglobinopathies.

Natural history models

For 14 causes in the GBD 2010, we have used natural history models because cause of death data systems do not capture sufficient information. The natural history model for African trypanosomiasis was updated to reflect more recent notification data. We included the most recently available case notification data from WHO (up to 2012). We have made substantial changes to the HIV natural history model which are discussed in detail in Murray et al.[25] Our congenital syphilis natural history model is estimated as in the GBD 2010, with updated data on antenatal care coverage to inform the number of births at risk and additional vital registration data sources to inform age and sex distribution of deaths. We also used simple natural history models for typhoid and paratyphoid fever, whooping cough, measles, visceral leishmaniasis, and yellow fever. In addition, because of extremely sparse vital registration data recording the specific type of hepatitis, we shifted to using a natural history models for all the detailed causes of hepatitis. The natural history model takes into account the extensive serological data on the prevalence of antibodies or antigens for hepatitis A, B, and C and more limited data on case-fatality rates.

Alzheimer's disease and other dementias were analyzed in GBD 2010 using CODEm. Because of the marked inconsistency between the data on prevalence and mortality, we changed our strategy to use a natural history model. Prevalence data do not show a substantial change over time while age-standardized mortality rates in high income countries have increased ranging from about 25% (Denmark, Switzerland, Norway) to 46% (Germany). The prevalence of dementia between countries varies by a factor of three while dementia mortality recorded in vital registration data and verbal autopsy studies varies by more than twenty fold. Based on these findings we argue that the variation in dementia mortality rates between countries and over time was likely influenced by changes in coding practices with increasing propensity to assign dementia as an underlying cause of death. To correct for this, we examined data from 23 high-income countries with high-quality vital registration systems to estimate the ratio of registered dementia deaths to prevalent cases. Using DisMod-MR we used the mean of these ratios as an estimate of excess mortality to estimate age and sex-specific mortality from dementia consistent with the meta-regression of prevalence.

Mortality from natural disasters and armed conflict

See the explanation above for how mortality from war and natural disasters are included in the mortality and cause of death estimation.

Combining results for individual causes of death to generate final estimates – CoDCorrect algorithm

In the GBD 2010, because single-cause models were developed for each cause, the final step was to combine these models into estimates that are consistent with all-cause mortality for each age-sex-country-year group. For each cause-specific model and for all-cause mortality, we had 1000 draws from the posterior distribution for each age-sex-country-year group. We combined causes by taking a

random draw without replacement from the posterior distribution of each cause and all-cause mortality. Each cause was rescaled by a scalar equal to the draw of all-cause mortality divided by the sum of the draws of individual causes. GBD 2010 induced a correlation of 1.0 between the sum of cause-specific and all-cause mortality. CoDCorrect was applied in a hierarchical fashion: first to level 1 causes and then to level 2 and level 3 causes. Level two causes were constrained to sum to the level 1 parent cause. Levels of this cascade were largely the same as used in GBD 2010 and were chosen based on consideration of the amount and quality of available cause of death data.

For GBD 2013, we have made slight modifications to this approach. Because testing showed no substantial effect of the 1.0 correlation between draws of all-cause mortality and the sum of individual causes and because each cause is modeled independently such that the ordering of draws across causes are unrelated, we have removed this assumption. Further, because the modeling of HIV through the GBD version of Spectrum uses relationships between incidence, CD4 progression and death that are age-dependent and antiretroviral therapy (ART) scale-up over time has had major effects, we modified the way HIV deaths are handled in CoDCorrect. We ran CoDCorrect for all causes and then computed the pre-CoDCorrect cumulative deaths over time and age and compared to the cumulative deaths post-CoDCorrect. This provided an overall scalar which we used to adjust the entire HIV epidemic. To avoid in any age-sex-country-year the sum of individual deaths exceeding all-cause mortality, we computed the difference between the cumulatively scaled HIV deaths and the CoDCorrect HIV deaths and added this difference to the estimate of all-cause mortality at the draw level.

Counterfactual etiologies

In GBD 2010, diarrhoea deaths and lower respiratory infection deaths were reported for pathogen-specific etiologies in tabulations that summed to 100% of each parent cause. Since publication of the GBD 2010, the GEMS study (Global Enteric Multicenter Study)[55], has been released which provided rich information on the relative risk of diarrhoea being related to different pathogens. The relative risk approach uses a different conceptual framework than the ICD approach of underlying cause. Underlying cause follows the more than 200 year history of health statistics of assigning each death uniquely to a single underlying cause category. The relative risk approach follows the approach used more generally for risk factors, where cause is assigned based on comparison to a counterfactual. Counterfactual attribution to specific risks or in this case pathogens do not necessarily sum to 100%; in fact they can sum to more or less than 100%. We have shifted based on the GEMS study and consultations convened among experts in both diarrhoea and LRI on October 2013 to reporting results for counterfactual etiologies. To estimate diarrhoea mortality attributable to different pathogens, the primary approach was to calculate the population attributable fraction for the pathogens including: rotavirus, *Shigella*, enteropathogenic *E coli*, enterotoxigenic *E coli*, adenovirus (enteric adenovirus), norovirus, *Aeromonas*, other *Salmonella* (non typhoidal *Salmonella*), *Cryptosporidium*, *Campylobacter,* and *Entamoeba*. The Miettinen formula which uses the distribution of pathogens in patients and relative risks of pathogens for diarrhoea provides a PAF for each pathogen and was used by recent studies[56],[57] The formula used is:

$$PAF_i = p_i(pathogen\ in\ patients)(1 - \frac{1}{odds\ ratio_i})$$

Where PAF_i is the population attributable fraction of diarrhoea due to pathogen *i*, p_i is the prevalence of pathogen *i* in patients with diarrhoea, and $odds\ ratio_i$ is the odds ratio of diarrhoea in those with the

pathogen. We used DisMod-MR to estimate from published studies of inpatients and community samples the proportion of patients in each age-sex-country-year detected with each pathogen. By using study-level covariates in the meta-regression, we obtained different estimates for inpatients and community samples. We assumed inpatients to be a proxy for severe diarrhoea and death. We reanalyzed a multicenter case control study, GEMS,[58] to estimate the odds ratio for each pathogen in a multi-pathogen model using conditional logistic regression. Regression models included fixed effects for a specific pathogen with interaction terms for three age groups (0-1, 1-2, and 2-6) to allow different odds ratio by age and interaction terms for different GEMS field sites (Kenya, Mali, The Gambia, Mozambique, India, Bangladesh, and Pakistan) to estimate site-specific odds ratios. For other countries in the region, the odds ratio used was the average of the odds ratios (in logarithm scale) of the countries with GEMS sites in that region. For countries in central and southern sub-Saharan Africa, the average of GEMS sites located in eastern and western sub-Saharan Africa were used. For all other countries in regions without GEMS sites, the average of all odds ratio was used. In order to produce odds ratio uncertainty while averageing odds ratio, we generated 1,000 draws of joint normal distribution using a covariance matrix from the conditional logistic regression for each of the GEMS countries in a region. To produce the draws for non-GEMS countries, we selected draws from each of the GEMS countries until we had a full set of 1,000 draws. For example, to generate 1,000 draws for countries in eastern sub-Saharan Africa, we utilized draws from Kenya and Mozambique – the two GEMS countries within that region. We pulled 500 of the Kenya draws and 500 of the Mozambique draws in order to produce our full set of 1,000 draws that were used for all the other countries within this region. As GEMS only studied diarrhoea in children younger than five years, we applied the odds ratio of pathogens calculated for children aged two to five years of age when calculating adults. We did not assign diarrhoea cases or deaths to a pathogen for an age-country-year if more than 95% of draws were greater than 1.

For cholera, we used published literature and compared this with WHO case notification data to estimate under-reporting for cholera and ultimately to estimate the number of cases. First we compared the expected number of cholera cases for each country year from epidemiological studies that reported proportion of cholera in diarrhoea patients using the total number of diarrhoea episodes from a separate analysis. We assigned cholera PAFs to adjust the cholera cases. We modeled underreporting of cholera case notification and imputed for all countries to predict the total number of cholera cases for all countries present in WHO cholera notification. Furthermore, we modeled proportion of cholera in all diarrhoea cases in these countries to impute for all country-years from 1990 forward, giving us a final estimate of the proportion of cholera and ultimately the number of cholera cases by country and year. Up until this step, country estimates are for all ages combined. To split into age-specific cholera case estimates, we used a common age curve derived from a random effect meta-regression analysis (DisMod-MR); the age curve was derived from studies that reported the proportion of cholera in cases for multiple age groups. To estimate cholera deaths, we modeled cholera case fatality in DisMod-MR using published studies.

Clostridium difficile is not commonly studied as a cause of diarrhoea in children; we were unable to estimate the epidemiological PAF as we had for other pathogens, as *Clostridium difficile* was not included in the GEMS study. Because *Clostridium difficile* is related to the hospital and health care utilization, we found and used hospital data as the primary data source for estimation. We modeled the

incidence and case fatality of *Clostridium difficile* and assumed a one month risk of death[59] in DisMod-MR to estimate the number of deaths.

For GBD 2013, we have split lower respiratory infection (LRI) mortality into four etiological categories: Streptococcus pneumoniae, *Haemophilus influenza* type B (Hib) pneumonia, respiratory syncytial virus (RSV) pneumonia and influenza. The counterfactual approach captures the complex interactions between the LRI etiologies[60] and also excludes the "other LRI infection" category previously included in GBD 2010. Moreover, we did not attribute LRI to any etiology for children younger than one month. We have adopted a different estimation approach for bacterial and viral etiologies based on available data. For pneumococcal and Hib pneumonia, we estimated the etiological fraction using vaccine efficacy studies.[61–63] For pneumococcal pneumonia, we included data from controlled trials and observational studies such as before-after analyses of pneumococcal vaccine (PCV) introduction.[64–75] For Hib, we excluded case-control studies due to implausibly large vaccine efficacy estimates. Furthermore, unlike PCV, there was a paucity of data from vaccine efficacy studies on impact outside of child ages. As a result, we have not estimated the etiological fraction of Hib for LRI in ages five and older. Data were adjusted for efficacy using invasive disease as a marker as well as serotype coverage for PCV.[63] Pooled estimates of etiological fractions by age were estimated using DisMod MR for PCV and random-effects meta-analysis for Hib and were adjusted post-hoc for national-level coverage of PCV and Hib vaccine. For RSV and influenza, we relied on observational studies that measured etiological fractions amongst hospitalized LRI cases. Estimates of the etiological fractions among cases by country, age, and sex were determined using DisMod MR and using the odds ratio of exposure from case-control studies. To account for the higher case-fatality of bacterial versus viral LRI etiologies, we applied a relative case-fatality differential based on in-hospital case-fatality using hospital admissions that included cases coded to the specific pneumonia etiologies.

Convergence metrics

To test whether there is convergence in all-cause and cause-specific mortality among the 188 countries since 1990, we compute two measures: the average relative difference and the average absolute difference between any pair of countries included in the GBD2013 study. The average relative difference is also known as the Gini coefficient and is the most commonly used measure of inequality. For cross-country comparisons, we use the population-weighted version of the Gini coefficient in age-specific mortality rates so that small populations do not have an undue influence on the assessment of global mortality convergence.[76]

$$Gini = \frac{\sum_{i=1}^{N}\sum_{j=1}^{N}(|x_i - x_j|)p_i p_j}{2(\sum_{j=1}^{N} p_j)^2 \mu}$$

Where x_i is the metric of interest for country *i*, p_i is the population of country *i*, *N* is the number of countries, and μ is the mean across countries. Inspection of this equation shows that this can be interpreted as the average relative difference across all pairs of countries weighted for population size. In order for the Gini coefficient to decline, the percent decline in mortality for countries with higher mortality must in general be faster than for countries with lower mortality.

Another measure is to examine the average absolute difference across all pairs of countries weighted by population size, this measure has been used by demographers to also examine convergence across countries.[77] If every country declines at the same percent each year, this measure will steadily decline. The equation for the population-weighted version of this is:

$$mean \quad absolute \quad difference = \frac{\sum_{i=1}^{N}\sum_{j=1}^{N}(|\ x_i - x_j\ |)p_i p_j}{2(\sum_{j=1}^{N} p_j)^2}$$

Where p_i and p_j represent national populations covered in the GBD2013 study. x_i and x_j indicate age-specific mortality rates for age groups 0, -14, 5-9, …, and 80 plus. We compute this for all-cause mortality for each age-group for 1990-2013 and for age-standardized rates for each cause. Average absolute difference can decline while average relative difference (the Gini coefficient) rises. The two metrics provide different perspectives on convergence.

Multiple decrement life tables

We used age-specific cause of death results and all-cause mortality life tables to compute the conditional probability of death for three summary intervals: childhood and adolescence (0 to exact age 15), reproductive-age adults (15 to exact age 50), middle-aged adults (50 to exact age 75), and the cause specific contributions to each of these summary indicators. For each conditional probability of death, we use multiple decrement life table method[78] to compute the probability of death from each cause and the overall contribution of each cause of death to the summary probability of death indicators for the three broad age groups using the equation below:

$${}_nQF_x^{\ i} = \frac{\sum_{x=X}^{N+X-5} l_x \bullet {}_5q_x^i}{\sum_{i=1}^{K}\sum_{x=X}^{N+X-5} l_x \bullet {}_5q_x^i}$$

Where ${}_nQF_x^{\ i}$ is the fraction of contribution to probability of death from cause *i* in age group *x* to *x+n*. l_x is the probability of survival from birth to age *x* and ${}_5q_x^i$ is the probability of death from cause *i* in age group *x* to *x+5*. To estimate the contribution of changes in cause-specific mortality to changes in global and regional life expectancy, we calculate the decomposition of changes in life expectancy by age and cause of death using the approach detailed by Beltran-Sanchez, Preston, and Canudas-Romo.[79]

Age-standardized rates and years of life lost

For GBD 2010, we computed age-standardized rates using the world population age-standard issued by WHO in 2001.[80] To reflect the substantial change in global demography since 2001, we have updated this standard. We used the same method as WHO and computed a standard population structure using population estimates for years 2010 to 2035 from the most recent World Population Prospects by the United Nations Population Division. Appendix table 6 (pp 95-96) provides the details on the GBD world population age-standard. We compute years of life lost (YLLs) by multiplying numbers of deaths from

each cause in each age-group by the reference life expectancy at the average age of death for those who die in the age group age following the standard GBD 2010 methods.[3] Key indicators from the new GBD standard life table are provided in appendix tables 9 and 10 (pp 121-140).

Ranking lists and decomposition analysis.

We use the GBD 2010 approach for creating ranked lists of specific diseases and injuries. The GBD 2010 ranking list was modified to incorporate newly estimated causes with the same overall assignment of rank causes as GBD 2010: typhoid and paratyphoid separately, hemolytic disease in fetus and newborn and other neonatal jaundice, mesothelioma, unintentional suffocation, pulmonary aspiration and foreign body in trachea or lung, and foreign body in other part of body. Following the methods developed by Lozano et al,[3] we decompose changes in the number of global deaths and global YLLs into the contributions from population growth, population aging and age-specific death rates.

Role of the funding source

The sponsor 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 the final responsibility to submit the paper.

Results

Global all-cause mortality

Global life expectancy at birth for both sexes increased from 65.3 in 1990 to 71.5 in 2013, an average increase of 0.27 years per calendar year. Increases over the 23 year period for females were 6.6 compared to 5.8 for males. Figure 4 shows the annual change in global life expectancy at birth, documenting the slowdown in progress in the 1990s with a marked drop due to the Rwanda genocide and famine in North Korea and the return to increases of about 0.3 years or more per year since 2003. If the median rate of change of the last 23 years were to continue in the future, by 2030 global female life expectancy would be 85.3 and male would be 78.1. Reduced fertility and the consequent demographic shift of the world's population to older ages has led to the mean age of death in the world increasing from 46.7 in 1990 to 59.3 in 2013. The global number of deaths in both sexes for all ages combined increased from 47.47 (46.77-48.22) million in 1990 to 54.86 (53.57 – 56.34) million in 2013, partly due to consistent increases in global population over the past decades. More rapid declines in child death rates compared to other age-specific death rates have led to a shift in the age structure of global deaths with substantial proportional decreases in children, which went down in absolute terms from 12.11 (11.94 – 12.29) million in 1990 to 6.28 (5.98 – 6.60) million in 2013, and large increases in the proportion of deaths over age 80 (figure 5). Figure 5 also shows the breakdown of death numbers by super-region and highlights the reductions in the number of child deaths over the period in south Asia and southeast Asia with very substantial percentage declines in north Africa and the Middle East along with Latin America and the Caribbean. However, the number of child deaths in sub-Saharan Africa only changed from 3.68 (3.63 – 3.73) million in 1990 to 3.20 (3.00 – 3.42) million in 2013. Substantial increases in the number of deaths over age 80 have occurred in high-income regions as well as in southeast Asia and south Asia.

Rising global life expectancy at birth has not come from uniform progress across age-groups or countries. Figure 6 provides information on the percentage change in global age and sex-specific death

rates and two metrics on the distribution of mortality rates across countries. The x-axis in figure 6 shows the relative change in population-weighted mean country-level age-specific mortality rates by sex from 1990 to 2013. In all age-groups except the 80 plus age-group, there has been a larger percentage decline in mean mortality rate for females than males. Larger decline in males over age 80 probably can be attributed to the differences in the age composition between males and females in this open-ended age-group. The mortality rate in the under-five age group has declined much more over the interval than those in the older age-groups. The smallest declines have been observed for men in age-groups 30-34 to 35-39. The y-axis in figure 6 shows the change in the population-weighted average relative difference in age-specific mortality rates, also known as the Gini coefficient, for the same time interval. For all age-groups, these relative differences across countries (which we term inequality) have been increasing except in age-group 10-14 and 15-19 for females. The divergence in age-specific mortality rates is much more pronounced in young adult age groups between ages 20 and 44 for both males and females; dominant causes in these age-groups include HIV/AIDS, interpersonal violence, maternal mortality, and road injury. In the same graph, age-groups for which the average absolute difference in age-specific mortality rates have decreased from 1990 to 2013 are shown with hollow points and those where the average absolute difference has increased in solid points. For many age groups, in males and females, the absolute differences have been declining while at the same time relative inequality as measured by the Gini coefficients have been increasing. For females between ages 25-39 and 75 and over, and for males between ages 20 and 49 and 65 and over, both relative and absolute differences in mean age-specific mortality rates have been increasing since 1990.

Global causes of death

Using multiple decrement life tables, we have decomposed change in global and regional life expectancy into contributions from changes in large cause groups (level 2 of the GBD cause hierarchy) shown in figure 7. This highlights differences between two time points, 1990 and 2013 but does not provide information on non-linear trends during the intervening years. Between 1990 and 2013, global life expectancy at birth increased by 6.2 years for both sexes combined (5.8 years for males; 6.6 years for females). The increase in global life expectancy from 1990 to 2013 resulted particularly from decline in mortality from lower respiratory infections and diarrhoeal diseases; cardiovascular and circulatory diseases; neonatal conditions; cancers; and chronic respiratory diseases, which contributed roughly 2.2, 1.1, 0.7, 0.4, and 0.5 years, respectively. Declines in mortality from unintentional injuries added another 0.3 years to life expectancy, while female life expectancy increased by about 0.2 years due to reductions in maternal mortality since 1990. These gains were marginally offset by increased mortality from diabetes, chronic kidney diseases, and related conditions, as well as musculoskeletal disorders, although the net effect of these increases in mortality was small, reducing life expectancy, on average, by about 0.1 years. Figure 7 also shows the contribution of different causes to changes in life expectancy in the 21 GBD regions. Five main causes have reduced life expectancy in some regions: HIV/AIDS caused major reductions in southern sub-Saharan Africa and much smaller reductions in western and eastern sub-Saharan Africa; diabetes, chronic kidney disease and other endocrine disorders made a negative contribution to life expectancy across many regions, most notably in Oceania and Central Latin America; mental disorders and substance abuse made a negative contribution in multiple regions, especially High-Income North America; intentional injuries reduced life expectancy in South Asia, High-Income Asia Pacific, and sub-Saharan Africa; and cirrhosis made a negative impact in Eastern Europe and Central Asia. Large gains in life expectancy in sub-Saharan Africa have been driven in a large part by reductions

in diarrhoea and lower respiratory infections and reductions in neonatal disorders. Gains in developed regions are driven more by reductions in cardiovascular disease, some cancers, transport injuries and chronic respiratory conditions.

Table 3 provides estimates of the number of deaths for both sexes and all ages combined in 1990 and 2013 for 240 causes along with age-standardized death rates. We find that over the last 23 years there has been a steady shift towards increased numbers of deaths from non-communicable diseases and injuries and reductions in death numbers from communicable, maternal, neonatal, and nutritional causes. Examination of age-standardized rates, however, reveals that rates for all three broad categories of causes have been declining over the interval. The shift to non-communicable diseases, at least at the global level, is driven by faster rates of decline for communicable, maternal, neonatal and nutritional causes and an ageing world population.

In 2013, 11.8 (11.3-12.3) million deaths were due to communicable, maternal, neonatal, and nutritional disorders, 2.7 (2.4-2.8) million from lower respiratory infections, 1.3 million from each of HIV/AIDS, tuberculosis, and diarrhoeal diseases (1.3-1.5, 1.2-1.4, 1.2-1.4), 2 (1.9-2.2) million from neonatal conditions, 854,600 (702,924-1,032,497) from malaria, and 293,335 (261,322-328,200) from maternal causes, about 20% less than in 2000 - when they cumulatively accounted for 26.7 (26.0-27.5) million deaths. Comparing 2000 to 2013, deaths from diarrhoeal diseases have fallen by 31.1% (1.8 (1.7-2.0) to 1.3 (1.2-1.4) million), tuberculosis and meningitis each by about 20% (1.6 (1.4-1.7) to 1.3 (1.2-1.4) million, 377.3 (331.4-438.0) to 303.5 (261.4-346.3) thousand), while tetanus and measles mortality has declined by about 60% (142.4 (108.8-163.1) to 58.9 (39.8-77.3) thousand) and 80% (494.5 (279.4-763.8) to 95.6 (48.5-172.9) thousand) respectively and by about 40% for diphtheria (5.4 (2.8-10.7) to 3.3 (1.7-6.6) thousand) and whooping cough (111.8 (42.3-242.4) to 60.6 (22.3-136.8) thousand). Deaths from neonatal causes have declined by 26% since 2000 (2.8 to 2 million), and by about one-fifth for maternal causes since 2000 (364.9 to 293.3 thousand). Comparing 2013 to 1990, malaria deaths decreased by 4.4% (888.1 to 854.6 thousand) and HIV/AIDS increased by a massive 368% (286.4 thousand to 1.3 million). Both malaria and HIV/AIDS increased to a peak level of mortality around 2005 (1.7 (1.6-1.9) million, 1.2 (1.1-1.4) million); HIV/AIDS declined 21% (21.5-20.4%) from 2005 to 2013 and malaria by 30% (35.4-24.8%).[38] The risk of death from various leading causes within this category of diseases and conditions, as measured by the age-standardized death rate (see table 3), has generally declined by an even greater amount. Age-standardized death rates for the category as a whole, as well as for lower respiratory infections, maternal, and neonatal disorders, have all declined by about 40% since 1990 (66.8 to 41.7 per 100,000, 6.9 to 3.9 per 100,000, 46.9 to 27.6 per 100,000), and by between 50% and 60% for tuberculosis (43.5 to 19.4 per 100,000), diarrhoeal diseases (47.4 to 19.0 per 100,000), and several specific neglected tropical diseases. Despite the small decrease in numbers of deaths, the age-standardized malaria mortality rate worldwide has fallen by 19% since 1990 (14.6 to 11.9 per 100,000), with much of that decline occurring in the last five years or so.

A pattern is evident for most of the leading non-communicable diseases: deaths are increasing but age-standardized rates are declining. Annual deaths from this category rose by 42% between 1990 and 2013, claiming 27 (26.3-27.6) million lives in 1990 and 38.3 (37.2-39.4) million in 2013.Allowing for changes in the age structure of the world population between 1990 and 2013, age-standardized death rates from

non-communicable diseases actually fell by 18.6% (782.5 to 637.5 per 100,000) - 22% for the collective of cardiovascular and circulatory diseases (375.5 to 293.2 per 100,000), 13-15% for cirrhosis of the liver (21.8 to 18.8 per 100,000) and cancers (157.0 to 133.8 per 100,000), and by 22-30% for other digestive diseases (2.3 to 1.8 per 100,000) and chronic respiratory diseases (104.5 to 73.0 per 100,000). For many specific conditions, including stomach cancer (21.7 to 13.8 per 100,000), Hodgkin lymphoma's disease (0.8 to 0.4 per 100,000), rheumatic heart disease (9.8 to 4.4 per 100,000), peptic ulcer disease (9.1 to 4.9 per 100,000), appendicitis (2.0 to 1.1 per 100,000), and schizophrenia (0.6 to 0.2 per 100,000), age-standardized death rates have fallen by more than one-third since 1990. Age-standardized death rates from some important sites of cancer such as lung, breast, and leukemia, have declined by 9% (29.6 to 27.0 per 100,000), 18% (9.0 to 7.4 per 100,000), and 20% (5.2 to 4.1 per 100,000), respectively, but have remained unchanged for others, including liver (13.7 to 13.0 per 100,000), kidney (2.1 to 2.2 per 100,000), lip and oral cavity (2.3 to 2.1 per 100,000), pancreas (5.4 to 5.9 per 100,000) and prostate (5.1 to 5.2 per 100,000), as well as for non-Hodgkin's lymphoma (3.5 to 3.6 per 100,000).Notably, global age-standardized death rates from ischemic heart disease and stroke have fallen by more than one-fifth since 1990 (177.3 to 137.8 per 100,000, 141.6 to 110.1 per 100,000), and by about 42% from asthma (13.7 to 8.0 per 100,000).

Only for a handful of diseases have age-standardized death rates increased significantly at the global level from 1990 to 2013. The largest increase has been for HIV/AIDS, in fact HIV/AIDS mortality peaked in 2005 and the age-standardized death rate declined 31% (25.7% to 35.9%) from 2005 to 2013 (26.9 to 18.5 per 100,000). Among the cancers, only liver cancer due to hepatitis C has seen a significant increase, going up 125% (2.4 to 5.5 per 100,000). While cardiovascular and circulatory diseases' age-standardized rates have declined by 22% (375.5 to 293.2 per 100,000), there have been significant increases in atrial fibrillation and flutter and peripheral vascular disease. Alzheimer's disease and other dementias has increased following the revised methods of GBD 2013 by only 3.2% (28.9 to 29.9 per 100,000) and Parkinson's by 28.2% (1.5 to 1.8 per 100,000) Important increases at the global level have occurred for diabetes (9%, 19.8 to 21.6 per 100,000) and an even larger increase for chronic kidney disease (36.9%, 11.6 to 15.8 per 100,000). Sickle cell age-standardized death rates have increased while other hemoglobinopathies have declined. The residual category of endocrine, metabolic, blood, and immune disorders have increased by 11.6% (2.7 to 3.0 per 100,000).

Age-standardized death rates from injuries (21% decline, 88.5 to 70.0 per 100,000) and from most specific causes of injury death have also declined since 1990, but typically much less than for diseases. Transport injury age-standardized death rates have remained relatively unchanged since 1990, causing 1.48 million deaths in 2013, mostly (1.40 million) from road injuries. The number of deaths from unintentional injuries as a whole (2.01 million) has remained essentially unchanged since 1990, although age-standardized death rates have fallen by more than one-quarter (40.8 to 30.4 per 100,000). Particularly large declines in mortality rates have occurred from drowning (46%, 9.4 to 5.2 per 100,000), fires (42%, 5.9 to 3.5 per 100,000), suffocation (60%, 1.2 to 0.5 per 100,000) and venomous animal contact (49%, 1.5 to 0.8 per 100,000). Age-standardized death rates from self-harm have also fallen by 23% (15.8 to 12.2 per 100,000), while interpersonal violence dropped by 16% (6.6 to 5.6 per 100,000). Among injuries, only falls, foreign body in other body part, and adverse effects of medical treatment have seen rising age-standardized death rates, but these are not statistically significant.

Table 4 decomposes change in the number of global deaths for Level 1 and Level 2 causes in the GBD cause hierarchy into population growth, population aging and changes in age-specific rates. The key observation from this analysis is that while the number of deaths for NCDs and injuries are increasing overall and for nearly every Level 2 cause within these broad categories, age-specific death rates are declining for nearly all. Notable exceptions where numbers of deaths are increasing driven by contributions of population growth, aging and age-specific death rates include neurological disorders, Diabetes, urogenital, blood, and endocrine diseases and musculoskeletal disorders.

Figure 8 provides a summary of convergence metrics for Level 1 and Level 2 causes in the GBD cause hierarchy for both sexes combined. Because narrowing relative or absolute differences would be undesirable if they came about from rising mortality rates, figure 8 also includes the percent change in the age-standardized death rate. For each metric the results are colored to highlight statistically significant improvement (green), significant worsening (red), and insignificant change (yellow). For only three Level 2 causes are the rates increasing significantly: neurological disorders; diabetes, urogenital, blood, and endocrine diseases; and musculoskeletal disorders. Increases in the latter category are driven by the category other musculoskeletal disorders; causes with high number of death in this category are systemic lupus erythematosus, systemic sclerosis [scleroderma], pyogenic arthritis, and chronic osteomyelitis. The average relative difference between countries (the inter-country Gini coefficient) ranges from 0.76 for neglected tropical diseases to a low of 0.13 for non-communicable causes. Average mean differences in the age-standardized rates between countries ranges from 59.97 for cardiovascular and circulatory diseases to 0.32 for musculoskeletal disorders. In general, there is much greater inequality in the communicable, maternal, neonatal, and nutritional causes than for non-communicable causes or injuries. A very important exception to that general pattern is war and disaster which are extraordinarily unequally distributed across countries. There is no cause for which the age-standardized death rate is declining and the two convergence metrics are improving significantly from 1990 to 2013. For many communicable, maternal, neonatal, and nutritional causes, rates are declining, mean absolute differences are decreasing but relative differences are increasing. For neoplasms, chronic respiratory diseases and digestive diseases, rates are declining, mean absolute differences are declining and relative difference is not significantly different than zero. The same is observed for unintentional injuries.

Global causes of child death

Table 5 provides figures for 1990 and 2013 for an abbreviated list of the major causes of child death. We have divided child causes into those occurring under one month and those between one month and 59 months. The number of neonatal deaths declined from 4.5 (4.4-4.6) million in 1990 to 2.6 (2.5-2.7) million in 2013, a 42% (45% - 39%) decline. The most important causes of neonatal death in 2013 are preterm birth complications (693 (553-853) thousand), neonatal encephalopathy (611 (492-724) thousand deaths), followed by neonatal sepsis (342 (215-479) thousand), congenital anomalies (247 (219-280) thousand), and lower respiratory infections (196 (169-225) thousand). Causes with more than a 50% reduction in the number of neonatal deaths include tetanus, diarrhoeal diseases, lower respiratory infections, preterm birth complications and congenital syphilis. Neonatal sepsis is notable for a statistically non-significant change from 1990 to 2013.

For children aged one to 59 months, the global number of deaths has declined by 52.0% from 1990 to 2013, going from 7.6 (7.4-7.8) million in 1990 to 3.7 (3.4-3.9) million in 2013. Communicable, neonatal,

and nutritional causes account for 75.5% (71.3-78.9%) (2.8 (2.5-3.0) million) of deaths in 2013, the remainder from non-communicable diseases and injuries. Two causes in this age-group each account for more than half a million deaths and collectively account for 34.9% (31.5-38.9%) of deaths: lower respiratory infections (709 thousand), and malaria (570 thousand). Four causes account for less than 500 thousand but more than 100 thousand deaths: diarrhoeal disease (475 thousand), meningitis (121 thousand), congenital anomalies (249 thousand), and nutritional deficiencies (261 thousand). Another seven causes each cause between 50 and 100 thousand deaths: drowning, syphilis, measles, whooping cough, intestinal infectious diseases, HIV/AIDS, and road injuries. More than 50% reductions in deaths between 1990 and 2013 have been observed for diarrhoeal diseases, lower respiratory infections, meningitis, whooping cough, tetanus, measles, preterm birth complications, and drowning. Of the causes detailed in table 5, only HIV/AIDS had a significant increase from 1990 to 2013 (81.1%, 35.2 to 63.8 thousand) although from 2005 to 2013 deaths declined from 25.95 (24.54-27.50) per 100,000 to 9.83 (9.01-11.04) per 100,000. In developed countries cancers account for 5.86% (5.06-6.66%) of deaths for children under-five while still only 1.02% (0.89-1.16%) in developing countries.

Figure 9A shows death rates under one month broken down into 19 selected major cause groups (that are mutually exclusive and collectively exhaustive) for the 21 GBD regions and figure 9B shows the same analysis for deaths between one month and 60 months. Note the rates for the neonatal period are for person-years. Because each infant is only exposed to at most one person-month, rates in that period are high compared to the period one to 59 months. Across regions, there is marked variation in the death rates from preterm birth complications, neonatal encephalopathy (birth asphyxia and birth trauma) and other neonatal disorders/jaundice. In addition, lower respiratory infections, HIV/AIDS, congenital syphilis, and malaria have an important contribution. Congenital anomalies range over five-fold from a high in central sub-Saharan Africa to a low in high-income Asia Pacific. Figure 9B shows that eastern, central and western sub-Saharan Africa have markedly higher death rates between 1 month and 59 months compared to other regions including south Asia. These higher rates are largely related to malaria, diarrhoeal diseases, measles, and nutritional disorders.

Global YLLs

Figure 10 shows a comparison of the 50 leading causes of global YLLs for both sexes combined in 1990 and 2013 with communicable, maternal, neonatal and nutritional causes highlighted in red, non-communicable causes in blue and injuries in green. Because of the way YLLs are computed, they give greater emphasis to causes of death at younger ages. The crossing lines are notable for dramatic declines in measles, meningitis, tetanus, syphilis, and whooping cough. Large increases are evident for road injuries, HIV/AIDS, diabetes, chronic kidney disease, colorectal cancer, Alzheimer's disease and other dementias, breast cancer, and cardiomyopathy and myocarditis Among the top 10 causes in 1990, nine remain in the top 10 in 2013 with HIV/AIDS moving in and tuberculosis moving to 11th. In terms of the percent increase in YLLs, the largest increase over the 23 year period were for HIV/AIDS (343.97, 245.48-444.17), atrial fibrillation and flutter (211.89, 182.55-242.63), peripheral vascular disease (119.79, 101.04-136.78), drug use disorders (119.22, 83.77-140.02), Parkinson's disease (101.64, 59.87-113.31), decubitus ulcer (93.34, 58.66-127.67), chronic kidney disease (89.60, 73.88-103.45), Alzheimer's disease and other dementias (89.43, 80.67-102.70), interstitial lung disease and pulmonary sarcoidosis (86.48, 25.63-193.79), and mesothelioma (83.62, 61.24-100.05).

It is important to identify key transition points in the comparative importance of different causes of premature mortality, in part to better inform program evaluation. Figure 11 shows annual estimates of YLLs for the top 25 leading causes either in 1990, or in 2013. Over this period, the rate of YLLs worldwide has fallen by about 30% (37,021.0 to 24,493.4 per 100,000), being more pronounced for Group I conditions (45% decline, 16,758.3 to 9,201.6 per 100,000) compared with non-communicable diseases (25%, 16,139.7 to 12,379.5 per 100,000) and injuries (30%, 4,122.9 to 2,912.3 per 100,000). Recent progress with disease control programs to prevent mortality from HIV/AIDS and malaria is clearly visible, as is the substantial and steady progress to prevent child deaths from neonatal disorders, diarrhoeal diseases, and lower respiratory infections; YLLs from these diseases have fallen by 40-65% since 1990. The success of vaccination programs since 1990 can also be seen from figure 11, with YLLs from measles and tetanus in particular now at very low levels. Specific trends for major non-communicable diseases are much less evident, with incremental declines from several leading causes of cancer, as well as from major vascular and chronic respiratory diseases, contributing to the 30% reduction in YLLs since 1990 (37,021.0 to 24,493.4 per 100,000). With the exception of drowning, only modest progress in reducing premature mortality from other leading causes of injury death has been achieved over the past few decades, with the impact of the 1994 genocide in Rwanda clearly visible.

Diarrhoea and lower respiratory infection etiologies

In 2013 there were 1.3 million deaths (1.2-1.4 million) caused by diarrhoea, showing a 51% (46-56%) percent decline since 1990 (2.6 million deaths [2.4 – 2.7 million]) (table 3). Rotavirus was the main cause of diarrhoea in under five children and was responsible for 23.5% (20.1-27.2) of total diarrhoea deaths or 122,000 (96,000-152,000) deaths in 2013, a slight decrease in the population attributable fraction (PAF) since 1990, followed by cholera with 8.7% (4.5-12.7%) (45,200 [23,410 – 67,553] deaths), *Cryptosporidium* with 6.8% (5.1-9.3%) (35,162 [25,874 – 48,156] deaths) and shigellosis with 6.4% (5.1-7.9) (33,390 [24,877 – 43,453] deaths) of total diarrhoea deaths. At least 68% of diarrhea in 2013 was unexplained by these pathogens, an increase from 48% in 1990 (table 6). The distribution of *Shigella* and *Aeromonas* in patients showed a significant ecological association with sanitation and along with non-typhoid *Salmonella*, caused an overall 5.4% (28,062 deaths) decrease in deaths since 1990. Rotavirus is the most important pathogen with a 35-41% PAF (967-104 deaths) in east/southeast Asia and eastern Europe for children under age five; though it is the lowest PAF in high-income North America and the Caribbean. *Shigella* is an important pathogen in North Africa and the Middle East and Oceania (19.4% [11.8-29.4], 3790 [1976 – 6381] deaths and 13.9% [9.5-19.3], 118.4 [45.4 – 249.6] deaths), respectively), *Cryptosporidium* in sub-Saharan Africa, cholera in central sub-Saharan Africa and Andean Latin America, and enterotoxigenic *E coli* was consistently an important cause of diarrhoea death around the world. *Campylobacter* did not have a significant epidemiological relationship with diarrhoea in the majority of countries and was an important cause only in some age groups in the GEMS data in India, Bangladesh, and Mozambique. We estimated a great proportion of death caused by *Clostridium difficile* in western Europe, high-income North America, high-income Asia Pacific, and Australia with greater than 45% of diarrhoea deaths, ranging from 8 deaths in Australasia to 71 in western Europe, and to a lesser extent in central and eastern Europe (20.1% [14.0-27.1] or 16 [14-19]

deaths, and 19.0% [12.6-26.6] or 47 [38-57] deaths respectively). Cholera was responsible for 45,000 (23,000-68,000) deaths in under five children where the majority of deaths (76% or 34,000 deaths) happened in central and eastern sub-Saharan Africa and south and southeast Asia. Cholera was the third leading cause of diarrhoea for all ages, with 70,000 deaths (38,000, 97,000) or 5.5% (3.0, 7.7) of all diarrhoeal deaths, behind Rotavirus, with 177,000 (140,000, 218,000) 14.0% (11.4, 16.6), and Shigellosis, 74,000 (59,000, 94,000) 5.8% (4.7, 7.3). *Clostridium difficile* is particularly important in adults in western developed countries and Australia, where as high as 90% of diarrhoea death in the elderly was caused by it.

Globally in 2013, pneumococcus was responsible for the largest number of LRI deaths in children under five (264,000 [156,000, 366,000] deaths or 29.2% [18.0, 39.2] of all LRI deaths under the age of five), followed by *Hib* (109,000 [-10,000, 227,000] deaths or 12% [-1.1, 25.5] of all LRI deaths under the age of five), RSV (41,000 [23,000, 66,000] deaths or 4.5% [2.6, 7.1] of all LRI deaths under the age of five) and influenza (15,000 [6,000, 30,000] deaths or 1.7% [0.6, 3.3] of all LRI deaths under the age of five). The fraction of LRI deaths in children under five attributable to *Hib* have declined substantially since 1990, reflecting the global scale-up of *Hib* vaccine with the largest declines in high-income regions and Latin America where vaccine coverage is highest. The fraction of LRI deaths in children under five attributable to pneumococcus has also declined in high-income regions such as western Europe, North America and Australasia, reflecting the scale up of PCV, but continues to account for a large fraction of under-five LRI deaths in eastern Europe and elsewhere. Importantly, a large number of LRI deaths attributable to the four etiologies occur in older age populations. Across all ages, pneumococcus was responsible for 594,000 (296,000, 970,000) deaths (22.4% [11.4, 35.9] of all LRI deaths), followed by *Hib* (109,000 [-10,000, 227,000] deaths or 4.1% [-0.4, 8.8] of all LRI deaths), RSV (105,000 [45,000, 188,000] deaths or 4.0% [1.7, 7.3] of all LRI deaths) and influenza (82,000 [54,000, 110,000] deaths or 3.1% [2.0, 4.2] of all LRI deaths).

Country-specific probabilities of death during childhood and young adolescence

We compute conditional probabilities of death for three phases of the life-cycle (children and young adolescents, reproductive-age, and middle-age) by country broken down by cause; conditional probabilities are a useful summary as the values are readily interpretable. Figure 12 shows the probability of death between birth and age 15 partitioned into the contribution from different causes of death for 188 countries in 2013. Countries are grouped by GBD regions. The probability of child and adolescent (ages 0-14 years) death varies dramatically across and within regions from a low of 3 per 1,000 in Iceland girls to a high of 179 per 1,000 in Guinea-Bissau boys. In the more demographically advanced (measured by the mean age of death, a metric of fertility and mortality change) regions of the developed world the probability of death is below 10 per 1,000 for both sexes in nearly all countries except Albania, Bulgaria, Belarus, Brunei, Moldova, Macedonia, Romania, Russia, and Ukraine. Causes of death are dominated by congenital anomalies and neonatal causes. In Southeast Asia, Malaysia has the lowest probability of death and Laos the highest with considerable mortality from lower respiratory infections, diarrhoea, and neonatal disorders. Drowning is an important cause of death for children in this region. In central Asia, probabilities of death range from 17 per 1,000 in Armenia to 65 per 1,000 in Turkmenistan with unusually high contributions from lower respiratory infections; drowning is also an important cause. In north Africa and the Middle East, Bahrain, Oman, and United Arab Emirates are all below 10 per 1,000 for girls, while Sudan and Yemen are over 40 per 1,000. Mortality in these countries

is dominated by congenital and neonatal causes. Pulmonary aspiration and foreign body in trachea and lung is unusually high in Bolivia based on the available vital registration data. In south Asia, the contribution of drowning in Bangladesh is notable but mortality is still dominated by neonatal causes, diarrhoea, and pneumonia in all the countries of the region with measles playing a role in Afghanistan. Throughout sub-Saharan Africa, the cause of death patterns are variable but malaria, HIV/AIDS, tuberculosis, nutritional deficiencies, and hemoglobinopathies play an important role in many countries. Mauritius, Seychelles, and Cape Verde all have much lower probabilities of death than other countries in this super-region. Countries with the highest probabilities of death in central and western sub-Saharan Africa have important contributions from malaria. Interpersonal violence is an important contributor to the probability of death in these age-groups in many countries of Latin America and several in southern Africa.

Country-specific probabilities of death during reproductive-ages

Figure 13 shows the probability of death in reproductive-age adults between exact age 15 and exact age 50 ($_{35}q_{15}$) partitioned by cause for 188 countries in 2013. Reproductive-age probabilities of death range from 12 per 1,000 for women in Andorra to 520 per 1,000 for men in Lesotho. In GBD developed regions, the probability of death is generally twice as high for men as for women. Across all countries, transport injuries makes an important contribution especially in men. Amongst men in developed countries, suicide and transport accidents make important contributions. In some countries, such as Norway and the United States, drug and alcohol use disorders account for more than 8% of the total probability of dying in this age interval for either sex. In central Europe, interpersonal violence is high in Albania, drug and alcohol disorders are notable in Bosnia, and cirrhosis in Bulgaria, Hungary, Poland, Romania, Slovakia, and Slovenia. In east Asia, liver cancer is an important cause of death. In southeast Asia, maternal mortality in Laos, Cambodia, Myanmar, and Timor-Leste stand out as important contributors for women. In men in the same region, interpersonal violence in the Philippines, Sri Lanka, and Thailand are notable; suicide in Sri Lanka also accounts for 22 per 1,000 probability of death. Other studies suggest interpersonal violence in the Philippines is concentrated in Mindanao.[81] Transport injuries are greater than 20 per 1,000 risk of death for men in Afghanistan, Cote d'Ivoire, Cameroon, Ecuador, Gabon, Guinea-Bissau, Equatorial Guinea, Kazakhstan, Mauritania, Nigeria, Oman, Sierra Leone, El Salvador, Thailand, and Uganda. Cirrhosis probability of death in Myanmar is 19 per 1,000 in males. Tuberculosis stands out in Cambodia, Indonesia, Laos, Myanmar and the Philippines in men. The gap between the probability of death for men and women is particularly large in eastern Europe and central Asia. The highest probability of death in reproductive-ages for men in these two regions is now in Mongolia. High probabilities of death for Mongolian men are a consequence of unusually high probabilities of interpersonal violence, self-harm, alcohol and drug use, cirrhosis, liver cancer, and tuberculosis. More generally in eastern Europe and central Asia men, there are major contributions from ischemic heart disease, self-harm, alcohol and drug use, cirrhosis, and tuberculosis; HIV plays an important role in Ukraine and Russia. In north Africa and the Middle East, transport injuries along with ischemic heart disease are predominant. In women in the region, breast cancer and maternal mortality in Sudan and Yemen are also major factors. In Latin America and the Caribbean, there is the remarkable contribution of interpersonal violence in men exceeding 20 per 1,000 probability of death in Brazil, Colombia, El Salvador, Guatemala, Honduras, and Venezuela. Despite generally high violence in the region, Cuba, Costa Rica, Bolivia, and Peru stand out as having low probabilities. In men, probabilities of death due to HIV/AIDS exceed 10 per 1,000 in Belize, Haiti, Saint Vincent and the Grenadines, the

Bahamas, Grenada, Guyana, Suriname, and Trinidad and Tobago. Cirrhosis contributes more than 10 per 1,000 to the probability of death in men in Guatemala, Mexico, and Guyana. Cervical cancer is a larger contributor to the probability of death than breast cancer in eight countries of Latin America and the Caribbean (Bolivia, Ecuador, Guatemala, Nicaragua, Peru, Paraguay, El Salvador, and Venezuela). Probabilities of death for men and women in Afghanistan are more than two-fold higher than other countries in the region; in women maternal mortality is the largest cause. In Oceania, Samoa and Tonga have much lower probabilities of death than other countries in the region. Throughout sub-Saharan Africa, there are major contributions in women from maternal mortality, HIV/AIDS, and tuberculosis. For men in the region, HIV/AIDS, tuberculosis, and transport injuries dominate in most countries. Liver cancer is also a major factor particularly for men in western sub-Saharan Africa.

Country-specific probabilities of death for during middle-age

Figure 14 shows the probability of death in middle-age from exact age 50 to exact age 75 ($_{25}q_{50}$) for men and women partitioned by cause. Middle-age probabilities of death range from 103 per 1,000 for women in Andorra to 763 per 1,000 for men in Lesotho. In all countries, ischemic heart disease and stroke are important contributors to the risk of death in middle-age, greater for men than women. Probabilities of death from ischemic heart disease range from 8 per 1,000 in Japan for women to over 240 per 1,000 in Belarus for men. In developed regions, lung cancer emerges as a major contributor to the risk of death for men. Breast cancer for women and prostate cancer for men also make notable contributions. Liver cancer in South Korea is greater than 20 per 1,000. In central Europe, large contributions from chronic respiratory diseases and cirrhosis are clear in Croatia, Hungary, Romania, and Slovenia. In some high-income countries, including Singapore, Argentina, and Uruguay, lower respiratory infections are recorded as important causes of death in these age-groups, more so in men than women. In southeast Asia, liver cancer, diabetes, and tuberculosis make larger contributions than in many other regions, particularly in Myanmar, the Philippines, Laos, Indonesia and Cambodia. Elsewhere in the region stroke, IHD, other cardiovascular and circulatory diseases, and chronic respiratory diseases are predominant. In all countries of eastern Europe and central Asia, stroke and ischemic heart disease in men and women are particularly prominent. Liver cancer in Mongolia is the highest in the world for these age-groups. Egypt has extraordinarily high cirrhosis mortality in middle-age for men and women particularly from hepatitis C. Deaths due to diabetes are particularly high in Morocco, Bahrain, Oman, and Qatar. In Central Latin America and the Caribbean, diabetes makes large contributions to causes of death in men and women; the highest probability of death in these regions from diabetes for males is 92 per 1,000 in Trinidad and Tobago and 84 per 1,000 for women in Guyana. Chronic kidney disease is particularly high in El Salvador, Mexico, and Nicaragua; more so in men than women.[74,75] In the Caribbean countries, diabetes, stroke, and ischemic heart disease account for 33.4% of the middle-age probability of death in Haitian men to 54.8% in Guyanese women. In all the countries of Oceania, diabetes accounts for an extremely large fraction of mortality in middle-age; in Papua New Guinea, chronic kidney disease is particularly important as a cause of death. For nearly all countries in sub-Saharan Africa, stroke and other cardiovascular diseases (which includes cardiomyopathies) are important. Diarrhoea and lower respiratory infections are also estimated to be important causes in nearly every country. Liver cancer in most countries of western sub-Saharan Africa is also important along with tuberculosis.

Country-specific leading causes of years of life lost (YLLs)

Figure 15 provides an integrated view of the leading causes of premature mortality across all age-groups for each country in 2013. It shows the ten leading causes of YLLs in each country. The global top 15 are

color keyed to help identify major country variation in the leading causes of YLLs. At the global level, the top ten causes now estimated are ischemic heart disease, lower respiratory infections, stroke, diarrhoea, road injury, HIV/AIDS, preterm birth, malaria, neonatal encephalopathy, and congenital causes. The differences between developed and developing countries are marked. Self-harm is the fourth cause of YLLs in developed countries and the 15th in developing. Lung cancer, Alzheimer's disease and other dementias, colorectal cancer, cardiomyopathies, breast cancer, stomach cancer, pancreas cancer, and diabetes are top 10 causes in the developed world but not in the top 10 in the developing world. Conversely, diarrhoea, malaria, HIV/AIDS, tuberculosis, preterm birth complications, neonatal encephalopathy, congenital and neonatal sepsis are in the top 10 in developing regions but not in developed. Country rank lists are organized by GBD super-region and region. Within high-income countries, the top three causes are ischemic heart disease, lung cancer, or stroke in 27 countries. More notable differences in the rankings across high-income countries are self-harm as the second cause of YLLs in South Korea, Alzheimer's disease and other dementias as the third cause in Finland and lower respiratory infections at the second and third cause in Singapore and Argentina, respectively. Cirrhosis is the third cause in Chile. Colorectal cancer is a top five cause in 13 high-income countries and diabetes in three high-income countries.

In central Europe, eastern Europe, and central Asia, ischemic heart disease and stroke dominate but in Serbia, Latvia, and Russia cardiomyopathies are also in the top five causes. Cardiomyopathies include alcoholic cardiomyopathies (146.2) especially in these regions. Reflecting comparatively higher child mortality within this region, Azerbaijan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, and Uzbekistan have preterm, or neonatal encephalopathy, in the top five causes. In eastern Europe, five causes (ischemic heart disease, stroke, self-harm, cirrhosis, and road injury) make up 49.7% (44.4% - 54.6%) (29.3 (28.4-30.2) million) of YLLs. In Latin America and the Caribbean, there is more variation in the leading cause of YLLs. Lower respiratory infections are the leading cause in Bolivia, Peru, Guatemala and Ecuador; HIV/AIDS in Haiti, interpersonal violence in Colombia, El Salvador, and Venezuela; stroke in Jamaica; congenital anomalies in Nicaragua, and ischemic heart disease in the rest. Road injury is in the top five for 17 of 29 countries. Diabetes is also in the top five for 13 countries. Chronic kidney disease is in the top five for Barbados, Costa Rica, El Salvador, Mexico, and Nicaragua. Perhaps most unusually, interpersonal violence is in the top five causes in 15 countries in the region; this is true in only one country outside Latin America and the Caribbean, namely South Africa.

In east Asia, the top five causes of YLLs in order are stroke, ischemic heart disease, road injury, COPD, and lung cancer. These are nearly the same top 5 as the United States, the only difference is Alzheimer's disease and other dementias which is fifth and road injury is sixth, providing evidence of epidemiological convergence between East Asian countries and some high-income countries. In Oceania, lower respiratory infections, diabetes, and diarrhoea are important. In Papua New Guinea, malaria is also a top five cause. Southeast Asia, Indonesia, Myanmar, and the Philippines have tuberculosis as a top five cause of YLLs. Road injury is a top five cause in Indonesia, Malaysia, Thailand, and Vietnam. Cirrhosis is in the top five in Myanmar and liver cancer in Thailand. Among the countries of south Asia, the leading causes are a mix of neonatal causes and ischemic heart disease, lower respiratory infections and stroke in most countries. Tuberculosis is the third cause in India.

In north Africa and the Middle East, in addition to ischemic heart disease and stroke, preterm birth complications, congenital anomalies, and road injury figure prominently in the leading causes of YLLs. In four countries – Oman, Qatar, Saudi Arabia, and United Arab Emirates – road injury is the leading cause of premature mortality. Cirrhosis is the third cause of YLLs in Egypt. Self-harm is in the top five in Bahrain, Qatar, and United Arab Emirates. The profile of leading causes of YLLs in sub-Saharan Africa is markedly different than the rest of the world with the exception of Mauritius and Seychelles. HIV/AIDS is the leading cause in 18 countries. Malaria is the leading cause in 14 countries. LRI is the leading cause in Angola, Comoros, Ethiopia, Madagascar, Rwanda, South Sudan, Cote d'Ivoire, Mauritania, and Sao Tome and Principe. Diarrhoea is the leading cause in Democratic Republic of the Congo (DRC), Eritrea, Somalia, and Chad. Tuberculosis is in the top five causes in 18 countries. Violence is the fifth cause in South Africa. Road injury is the fifth cause in Equatorial Guinea, Gabon, Botswana, Swaziland, Cameroon, and Nigeria.

Discussion

The GBD 2013 incorporates many new datasets on cause of death, particularly from China, and new data in 155 other countries. Compared to the GBD 2010 it provides the most comprehensive and up to date assessment of causes of death. The results for the GBD 2013 are based on re-estimation of all causes from 1990 to 2013 and thus supersede all previously published GBD time series. Publication of country level results provides many opportunities for benchmarking how well countries do compared to peers. At the broadest level our analysis of 240 causes for 188 countries confirms that global life expectancy at birth has continued to improve over the last 23 years and these improvements are driven largely by declines in diarrhoea, lower respiratory infections, neonatal causes in low-income countries and declines in cardiovascular diseases and some cancers in middle and high-income countries. HIV/AIDS particularly in southern sub-Saharan Africa has had a large enough effect to negate progress made in other causes contributing to declines in life expectancy. This general picture of progress masks enormous heterogeneity across countries and age-groups. Even within regions, there are markedly different levels of mortality, leading causes, and trends. Outside of sub-Saharan Africa, premature mortality is dominated by a relatively short list of causes including ischemic heart disease, stroke, lower respiratory infections, road injury, diarrhoea, preterm birth complications, neonatal encephalopathy, congenital anomalies, tuberculosis, COPD, cirrhosis, self-harm, and lung cancer. On top of these common causes, there is marked regional and country variation such as the dominant role of interpersonal violence in most countries of central Latin America and Brazil.

Our study points to extraordinary epidemiological progress: 157 of 240 causes show statistically significant declines over the period 1990 to 2013 in the global age-standardized death rate. The largest declines have been for some of the major communicable diseases including diarrhoeal diseases, lower respiratory infections, tuberculosis, measles etc. Age-standardized rates for many non-communicable causes are also declining. At the same time, 115 of these 240 causes, the number of deaths are increasing, driven by both growth in population and shifts in the population age-structure towards older ages. For a further 58 causes, changes in the age-standardized death rate over the 23 year interval are not statistically distinguishable from no change. For some of these causes, sparse data may be contributing to wide uncertainty intervals and in other cases uncertainty may be coming from inconsistent coding across countries. However, there are eight specific causes that account for more

than 100,000 deaths and for which age-standardized rates have increased significantly since 1990: HIV/AIDS, liver cancer due to hepatitis C, pancreatic cancer, atrial fibrillation and flutter, drug use disorders, diabetes, chronic kidney disease, and sickle cell disorders. Of these, three of them (HIV/AIDS, diabetes, and chronic kidney disease) account for more than a half a million deaths each. HIV/AIDS, however, has been declining as a cause of death since 2005. These causes, which run counter to an extraordinary global trend towards lower age-standardized death rates, deserve special attention. The rise and more recent fall of HIV/AIDS is well known as is the rise in diabetes. Increases for atrial fibrillation and flutter, pancreatic cancer, drug use disorders, and chronic kidney disease have received far less global attention. Drug use disorders and chronic kidney diseases are causing much greater death in some regions and countries. Nevertheless, they are important emerging global challenges that highlight the potential adverse effects of some behaviors and socio-economic developments. Given the important behavioural component for some of these causes, there is potentially an important role for public health policy and resources to modify these causes of death. These conditions, particularly HIV/AIDS and drug use disorders are also subject to social stigmatization which add an important challenge for effective policy interventions. Although very few causes have increasing age-standardized rates at the global level, there is remarkable and important variation in trends across countries such that causes with declining global age-standardized rates may be increasing in some countries, for example, ischemic heart disease in China.

Convergence or divergence?

Ambitious goals have been articulated for maternal and child mortality[82–84] such as the end of preventable maternal and child death in a generation. The Lancet Commission on Investing in Health has argued that a grand convergence in levels of health is possible between high, middle, and low-income countries.[26] Trends in the past 23 years provide an important starting point for framing how great a challenge achieving these aspirations will be and the political will and financial resources required. Part of the answer depends on how the goals are framed; for example, what does convergence mean? In the development literature on economic convergence, [85–87] convergence has been framed in terms of poverty rates or in terms of income inequality measured by the Gini coefficient or other metrics of inequality. A literature on convergence in life expectancy has tended to focus on measures of absolute difference[88–90] rather than relative difference.[91] In our analysis, there is unequivocal divergence in mortality rates for females 25-39 and 80 plus and for males 20-44 and 65 and older, similar to what Moser and colleagues found in the divergence of life expectancy at birth since the 1980s.[77] In these age-groups, both the Gini coefficient and the mean absolute difference in death rates are rising. In all other age-groups, except females 10-14, relative inequality is increasing but the absolute gap is narrowing. Framing a grand convergence as simply achieving a reduction in the differences in mortality rates across countries may not be sufficiently ambitious to meet the goals of many national policy makers. If all countries decline at the same percent per year, absolute difference will decrease and relative differences will stay constant. If the worst off countries have death rates that are 10 times higher than the best off and this ratio stays constant or worsens, many may not view that as convergence. For age-groups where the world is diverging both in terms of relative and absolute differences in death rates, extraordinary efforts will be required to achieve laudable goals such as a grand convergence. If convergence includes reducing the ratio of the worst to the best off, even for under-five mortality, convergence will require major new efforts to have faster percent declines in those countries with higher mortality.

Arguments that convergence is technically and financially feasible are grounded on the success of some countries in achieving rapid improvements.[26] From 1990 to 2013, for example, 13 countries, all low-income, achieved increases in life expectancy greater than 10 years. The real challenge is whether the routes to low mortality used by these countries are generalizable or transferable to those countries who currently are making the least progress. The Lancet Commission on Investing in Health drew attention to the four Cs (Cuba, Costa Rica, Chile, and China). Of this set China and Chile have demonstrated in the last 23 years a pace of progress in improving life expectancy faster than the global aggregate trend. The good news is that there are countries that were low-income in 1990 but have achieved remarkable progress in the last 23 years: Nepal, for example, has had an increase of 12.16 years achieving a life expectancy of 70.64 in 2013 for both sexes combined. Other examples of improvements greater than 12 years for both sexes combined include Rwanda, Ethiopia, Niger, the Maldives, Timor-Leste, and Iran. As the Rwandan genocide came after 1990, the progress from the peak of mortality during the genocide until 2013 is even larger, 49.63 years. Studies have already examined progress in Bangladesh, Ethiopia and Niger, particularly in reducing child mortality.[92] Further study of these countries may provide insights into the routes to low mortality, including the role of development assistance for health, rapid economic growth, and addressing chronic challenges such as famines. Simple assessments built up from individual technology analyses such as the Disease Control Priorities-2[93] assume a high-level of health system efficiency and contextual factors that are enabling of technology delivery such as levels of maternal education. Plans to achieve a grand convergence in the face of diverging mortality levels will need to take into account low levels of health system efficiency and low levels of health system resourcing in some countries and the greater efforts needed to achieve high intervention coverage in low-income countries with inadequate primary health care systems and low levels of educational attainment. The challenge of improving health system management, particularly at the local level, is a critical component of the route forward.

The analysis of average relative difference between countries (inter-country Gini coefficient) and average absolute difference between countries by cause reveals the general pattern that many communicable, maternal and neonatal causes along with war and natural disasters have far higher inequality across countries; all have average relative differences of more than 50%. Among the non-communicable disease categories, mental and substance use disorders is the only cause with a mean relative difference greater than 40%. Following the more stringent criteria for convergence, namely where global rates are declining and the Gini coefficient is declining, only cardiovascular and circulatory diseases and chronic respiratory diseases are converging. One implication is that as more countries go through the epidemiological transition, it appears likely that cross-country inequalities or relative differences for communicable causes will rise and inequalities for non-communicable causes will narrow. Narrowing inequalities across countries does not necessarily imply narrowing inequalities for NCDs within countries. Because mortality rises with age exponentially at least after age 50 relative differences at older ages where mortality becomes concentrated tend to be smaller. Causes such as diabetes, chronic kidney disease, and alcohol and drug use disorders where global rates are rising and inequality is increasing are a critical exception to this general pattern.

Non-communicable diseases

Age-standardized death rates due to cardiovascular and circulatory diseases have fallen in high-income and many middle-income countries since 1990. Particularly rapid declines have been seen in some countries between 1990 and 2013. For example, five countries, Bahrain, Israel, Denmark, South Korea, and the United Kingdom, had at least a 60% decline in age-standardized death rates due to ischemic heart disease. Many other countries have had declines between 40 and 60%. South Korea experienced a three-quarters reduction in age-adjusted death rates due to hemorrhagic stroke. However not all regions have experienced improvements. The decline in age-standardized cardiovascular death rates has been delayed until only recently in the region of the former Soviet Union. It is particularly concerning that China has seen almost no change in cardiovascular death rates over the past two decades while rates are increasing in South Asia. Over the same period of time, the ageing and growth of populations has led to an increase in the total number of cardiovascular deaths, accounting for 31.5% of all deaths globally in 2013, 17.3 (16.5-18.1) million. Ischemic heart disease, ischemic stroke, and hemorrhagic stroke continue to contribute the majority of cardiovascular and circulatory deaths in almost all countries. A notable exception is found in some Balkan countries, where cardiomyopathy appears to be a leading cause of death, possibly due to alcohol exposure or local patterns of garbage codes.[94] Additional studies will be needed to determine whether this finding is driven by medical certification practices or is related to alcohol or some other factor. Age-standardized death rates for atrial fibrillation and flutter and peripheral vascular disease have increased, possibly because of increased awareness of these conditions or better survival from cardiovascular diseases that share the same risk factors. Significant uncertainty remains for trends in mortality due to rheumatic heart disease, in part because endemic populations are concentrated within poorer subnational regions where data collection is limited and RHD may not always be coded as the underlying cause of death.[95, 95] Continued efforts to benchmark changes in cardiovascular and circulatory diseases will benefit from increasing access to verbal autopsy in India and sub-Saharan Africa, household surveys focused on chronic diseases, and improvements in electronic health records.

In general, cancer deaths are increasing but age-standardized cancer rates are declining. Some cancer related risk factors have been declining such as tobacco consumption but others such as obesity have been increasing. The substantial declines in cancers in general require further explanation. Four cancers have had increasing rates (non-Hodgkin's lymphoma, mesothelioma, kidney cancer, and pancreatic cancer); some explanations such as the potential link between the rise of diabetes and pancreatic cancer may account for some of these reversals. Because of differential rates of decline for other sites, the mix of cancers is steadily changing, particularly in developing country regions, such as the relative risk in importance of breast cancer compared to cervical cancer. These local cancer transitions have important implications for the development of cancer care programs and training. Because of the strong relationship between cancer mortality and age, ageing of the world's population is the most important driver of the rising number of cancer deaths in most countries. Most countries can expect to have to deal with larger numbers of patients who need diagnosis, treatment and palliation in the coming years.

Alzheimer's disease and other dementias

We have used a substantially different approach to estimate Alzheimer's disease and other dementia mortality in the GBD 2013 by focusing on studies of prevalence and using data from countries with the highest death to prevalence ratios in 2013 to estimate mortality in other regions and back in time. This shift dramatically lowers the increase in the age-standardized death rate for dementia although the numbers of dementia deaths nevertheless have increased 107.2% (94.9-124.0%) since 1990 (795.8 thousand to 1.7 million). Lower increases in the age-standardized rate are because the meta-regression of prevalence studies do not show a rapidly rising trend; one study, in fact, has reported declines in age-specific rates although our overall assessment suggests a slight increase in age-specific rates. [97] We are effectively arguing that even in high-income countries with complete medical certification of causes of death that dementia was systematically underestimated as a cause of death in earlier time periods. Other studies such as the National Mortality Followback Study in the US support this idea.[98] The misclassified dementia deaths may have been put into categories such as senility. Our garbage code redistribution algorithms used in the GBD 2013 for this broad garbage code may have been under-allocating to dementia in earlier time periods. In future research, we may want to more carefully trace to which garbage codes dementia deaths may have been assigned using hospital linkage or other approaches. The other effect of shifting to this approach is that we estimate considerably more dementia deaths in middle-income countries than estimated in the GBD 2010. Prevalence studies suggest there is dementia in these countries although it is rarely recorded on a death certificate as a cause of death. Our overall conclusion is that dementia is more common globally and that numbers are increasing due to population ageing with only a small component of the increase due to rising age-specific rates. The analysis of dementia will benefit from further population-based prevalence surveys, especially with repeated measurement over time using standardized definitions and methods. As further studies of this type become available and incorporated into the GBD, our estimates of dementia burden may be substantially revised. Trends in the category Alzheimer's disease and other dementias may mask upward trends in Alzheimer's and downward trends in vascular dementia; however, these are very difficult to tell apart in population-based prevalence studies and cause of death data. Nevertheless, our finding that the number of dementia deaths is increasing implies that governments should remain concerned about the rising demands for care that will come with population ageing even if future rates do not increase substantially.

Diarrhoea and Lower Respiratory Infections

Our results showed a significant heterogeneity in the distribution of the causes of diarrhoea around the world. A significant change has also happened in the distribution of pathogens since 1990 as seen for cholera in sub-Saharan Africa, where nearly 50% (20,343 [9,054 – 41,216] deaths) of all cholera deaths in children occur. Given that we have used GEMS data to estimate relative risks, it is perhaps not surprising that our results are comparable to their findings.[56] We found that the population attributable fraction for known pathogens such as *Campylobacter*, *Shigella*, and *Salmonella* are not significant in some countries and some ages. Because of the nature of case notification data, we had to estimate all types of cholera and were unable to break down cholera into O1, non-O1, and O-139. While diarrhoea deaths have decreased greatly from 1990 to 2013, the distribution of causes has changed slightly. In developed countries and adults, *Clostridium difficile* is an important threat that has been increasing during the past two decades. 65% (744,413 deaths) of unexplained diarrhoea above age five is an

important knowledge gap that needs researchers' attention. Lack of evidence for causes of unexplained diarrhoea is a big barrier to the control of diarrhoea burden and an important question for researchers and policy makers. Although the new counterfactual approach is successful in estimating attributable death empirically and adjusts for the overall pathogen load in the country, it still suffers from important limitations such as the potential low sensitivity of diagnostic tests. Some pathogens are more prevalent in controls than cases. This may present a distorted causal picture reported by experimental studies and travelers, but this is not seen in epidemiological studies due to continuous shedding of pathogen long after the acute phase.[99–103] These findings could also suggest a protective effect of infection from one or more pathogens against other pathogens or could be simply due to a differential decrease in the sensitivity of diagnostic tests (for other pathogens) where diarrhoea presents assuming a single pathogen caused the diarrhoea. More sensitive diagnostic tests help to improve sensitivity but at the price of decreased specificity due to contamination and post diarrhoea pathogen excretion. Follow up studies with multiple measurements of pathogens in children during healthy and diarrhoea periods may help to elucidate the true causal associations. Better case definition as well as more strict criteria for pathogens such as excluding recent diarrhoea cases can decrease exposure misclassifications.

Our estimates of the fraction of under-five LRI deaths attributable to the four pneumonia etiologies (pneumococcus, Hib, RSV, and influenza) are similar to previous estimates with pneumococcus and Hib being the predominant etiologies.[62,63,104–106] The continued large fraction of LRI attributable to pneumococcus and Hib, particularly in less developed regions where the absolute burden is highest, highlights the potential benefit of continuing to scale up PCV and Hib vaccine. It is important to note that these etiological fractions are computed using a counterfactual approach. This means that they do not add up to 100% but also that there may be overlap in the etiological fractions; for example, an LRI death may involve viral and bacterial co-infection. These results should also be interpreted with caution due to the underlying data used to generate these estimates. Data on etiologies are sparse and prone to a range of biases which is reflected in the large uncertainty intervals. Pneumococcal pneumonia mortality burden estimates in children rely on data showing disease reduction during vaccine probe studies using pneumococcal conjugate vaccines (PCV) in infants, as there are no sensitive diagnostics currently available to detect non-bacteremic pneumococcal pneumonia in children. To calculate burden in the absence of a diagnostic assay, the PCV probe studies need to assume a vaccine efficacy against non-bacteremic pneumonia caused by vaccine types, and this assumption has been an efficacy approximating that of protection from vaccine type bacteremia (75%). Recently released data from a large randomized trial of PCV in adults) have confirmed efficacy against bacteremic pneumonia of 75%, but efficacy against non–bacteremic pneumonia was only 45%.[107] If similar efficacy estimates are applied to infants, then the contribution of the pneumococcus to pneumonia mortality in infants may be as high as 63% (166,324 deaths). Due to sparse data, we did not estimate the etiological fraction due to Hib amongst the population aged five years and older. The before-after vaccine efficacy studies used to estimate the burden of pneumococcus were limited to high-income settings. These types of studies may also be biased due to underlying temporal trends in hospital admissions for LRI. Furthermore, the only variation included for pneumococcus and Hib reflects differences in coverage of PCV and Hib vaccine. The observational studies used for RSV and influenza were based on case series data from predominantly tertiary-level hospitals which may not be representative of the underlying population and are prone to varying case-definitions and diagnostic methods. Finally, hospital discharge data on the relative differences in case-fatality for RSV and influenza compared to pneumococcus and Hib were

limited to high and middle-income country settings. Several of these issues are being addressed by the Pneumonia Etiological Research for Child Health (PERCH) project[108] that is presently ongoing.

Injuries

The majority of global road traffic deaths occur in low and middle income countries and the numbers are rapidly increasing over time due to the growth in motorization. Mortality rates due to traffic related injuries in low and middle income countries are increasing. Pedestrians are most often affected, followed by car occupants and motorcyclists. A different pattern is observed for high-income countries where traffic deaths are decreasing. A similar divergence between low and high-income countries was observed for occupational injuries: in high-income countries a general decline was observed (with the notable exception of deaths resulting from asbestos-related mesotheliomas), whereas for low-income countries occupational injury deaths are increasing.

Suicide continues to be a major public health problem in many regions of the world. Half of all suicide deaths in the world occur in China and India alone. However, the trends are in opposite directions, decreasing rapidly in China but rising in India between 1990 and 2013. Both countries have experienced economic growth and urbanization, a key factor in limiting access to the very lethal pesticides, a common method of suicide by poisoning in both countries.[109] There must therefore be yet unexplained other reasons for this divergence in suicide rates between the two countries.

Several notable sharp increases in mortality due to war and disaster have occurred in recent years. Particularly, the 2010 Haiti earthquake, conflict in Syria over the past several years, the 2011 Tōhoku earthquake and tsunami in Japan, and conflict in Libya in 2011 have caused considerable loss of life. The war in Syria led to an estimated 29,947 (19,392 – 54,903) deaths in 2013, and about 10,504 and 21,422 in each of the two years prior. Uncertainty around these estimates is large, as several conflicting estimates exist. It is important to note that these are estimates of the direct deaths attributable to armed conflicts and natural disasters and are not an accounting of the full effects of shocks mediated through mechanisms such as the breakdown of health systems or critical infrastructure. For example the current conflict in Syria has had a significant impact on the routine immunization for polio, with the coverage now down to as low as 50% in some areas.[110] In reality, the estimation of direct deaths due to war and natural disasters is one of the more challenging components of the GBD measurement effort. We depend on the work of various groups to collate combatant reports, newspaper reports, humanitarian agency assessments and other direct accounts to approximate the number of deaths. Vital registration systems often do not function in war or conflict but may be more useful in countries with natural disasters as a way of measuring the number of fatalities. More work is needed in the future to better measure shock mortality.

India

India accounts for 19% of the world's deaths in 2013, 10.2 (9.3-11.4) million. Cause of death estimation for India is important both for health policy in India and for the global understanding of causes of death. India has also experienced remarkable progress in reducing both child and adult mortality over the last 23 years. Average annual rates of decline for adults have been 1.3% per year and 3.7% for children. Unfortunately, the availability of cause of death data is worse in 2013 than in 1990 or 2000. The Medical Certification of Causes of Death (CCD) system provides ongoing information on patterns of

urban mortality with better completeness in some states compared to others. In rural areas, the Survey of Causes of Death (Rural) routinely reported on causes of death using verbal autopsy from 1980 to 1998. The SCD was replaced with a verbal autopsy sample collected by the Registrar-General of India based on the ongoing Sample Registration Scheme. Data collected for 2002-2004 have been reported but not in full ICD detail – in fact, results have been released through a series of journal articles spanning 2008 to 2014 but even these have not provided the standard tabulation of deaths by ICD cause, age and sex used by most countries. Verbal autopsies have continued to be collected post 2004 but no data have been analyzed or released. Attempts to add verbal autopsy to other major data collection efforts of the government of India such as the Annual Health Survey and the latest round of the District Level Household Survey have so far been unsuccessful. Small community studies continue to be published but there is a major gap in our knowledge of rural cause of death patterns. Given rapid change in India, including declines in child and adult mortality, simple predictions based on the 2002-2004 data are inadequate. Our modeling strategy does take into account trends in key covariates that explain some changes in age-specific rates for many causes; nevertheless, more recent national data would be enormously helpful in developing more precise estimates of causes of death for India. Various epidemics such as Chikungunya, dengue, and H1N1 also point to the need for better ongoing surveillance of causes of death in India that does not suffer from long time lags.[111–114]

Comparing different global health estimates

Comparison of the GBD 2013 results with GBD 2010 for 1990 or 2010 reveals some important differences. The overall correlation coefficient of age-sex-country-cause rates for 1990 is 0.998 and for 2010 is 0.998. Although the correlation is extremely high, there have been, nevertheless, substantial percentage changes in some causes at the global level. The ten most important causes in terms of the change in the number of global deaths are Alzheimer's disease and other dementias, ischemic heart disease, interstitial lung disease and pulmonary sarcoidosis, cerebrovascular disease, neonatal encephalopathy due to birth asphyxia and trauma, lower respiratory infections, other cardiovascular and circulatory diseases, cirrhosis, malaria, and chronic kidney disease. These changes can be traced to several sources: new data, modifications of garbage coding algorithms and revised modeling strategies; some details on each of these are available in the appendix. In general, there has been a substantial increase in the data used: from 8,967 site-years to 14,236 site-years. Some specific changes are worth noting. First, there has been major expansion of data used in the analysis for China. Given China's population, the incorporation of extensive new cause of death data has led to important changes in China and these affect even global estimates. The five largest changes for China in 2010 compared to GBD 2010 results are ischemic heart disease, Alzheimer's disease and other dementias, cerebrovascular disease, interstitial lung disease and pulmonary sarcoidosis, and chronic obstructive pulmonary disease. Second, more detailed cause of death data covering 189 causes instead of 98 causes became available for the GBD 2013 for Russia. This affected a number of smaller causes such as those related to alcohol. Third, we have included new vital registration data for Turkey for years 2010 through 2012. Fourth, we chose to model India in two components, urban and rural, which allowed us to make much more use of some data sources such as the Survey of Causes of Death (Rural) for rural India. Given the large size of India, these changes have global impact. Fifth, for cancers, we have incorporated 1,145 registry-years of new data, including 128 from the recently released Cancer Incidence in Five Continents Volume X.[48] Sixth, the shift to using a Bayesian noise reduction algorithm for smoothing has limited the number of outliers, particularly in small verbal autopsy studies, some of which were included in the GBD 2010.

Seventh, important changes to garbage code redistribution algorithms, particularly the use of statistically derived algorithms that vary by region and country, have had important effects on injuries, cancers, and cardiovascular diseases. Other important changes include the treating of unspecified anemia as a garbage code whereas in the GBD 2010 it was mapped to iron-deficiency anemia, moving abdominal hernia from other digestive diseases to hernia, as well as moving deaths related to specific procedures to the category of adverse effects of medical treatment. In the GBD 2010 we included abdominal hernia, including umbilical hernia, ventral hernia, and diaphragmatic hernia in the category "other digestive diseases." In GBD 2013 we have combined these with inguinal hernia and femoral hernia into one cause named "hernia." In addition, we moved some ill-defined causes from the other digestive diseases category to more specific causes, thereby reducing the number of deaths in other digestive and changing the distribution of all digestive deaths amongst its more disaggregated causes. Seventh, the assessment of all-cause mortality in the GBD 2013 has benefited from both new data and improved approaches to assessing the age pattern of mortality in the model life table system. Finally, the much more detailed analysis of HIV/AIDS has led to major changes both in HIV/AIDS particularly in countries with concentrated epidemics, and in other causes, particularly in the reproductive ages and in countries with moderate to large epidemics.

The International Agency for Research on Cancer (IARC) produces cancer estimates by country, age, sex, and cancer cite for 2008 and 2012 (GLOBOCAN). Our definitions and the GLOBOCAN definitions are compatible for 25 sites. For these cancer sites, the total estimated prevalence number from GLOBOCAN is 6,848,204 in 2008 and 7,483,018 in 2012. In comparison, the GBD estimates for these years are 6,930,377 and 7,437,018, a 1.2% and 0.6% difference, respectively. At the global level, the largest variation in estimates occurs for thyroid, testicular, and other pharynx, with differences ranging from between 20% and 30%. The rough similarity of results at the global level masks substantial variation at the country level. Comparing age-standardized death rates for 2012, the correlation ranges from 0.94 for lung, bronchus and trachea to 0.20 for thyroid cancer. Five cancers have correlations below 0.5 (ovarian, non-Hodgkin's lymphoma, testicular, Hodgkin lymphoma, and thyroid). A further six cancer sites have correlations between 0.5 and 0.7 (uterine, nasopharynx, lip and oral cavity, breast, leukemia, and multiple myeloma). Given that both efforts use population-based cancer registry data and vital registration data as inputs, the wide variation in results requires explanation. As with all comparisons of different global health estimates, the differences stem from data, data processing and model development. We have included a wider range of registries than used by GLOBOCAN particularly in China and we have made use of the broader database of vital registration data. Our redistribution of cancer of unknown primary is based on a statistical model. The most important differences, however, likely stem from the modeling strategy. For all cancer sites in all countries, we have used CODEm. GLOBOCAN uses 9 different methods to estimate cancer mortality depending on the country.[115116] ; the choice of which method to apply can lead to surprising differences in estimated rates for neighboring countries without data. Illustrations of this problem include: the age-standardized death rate for male thyroid cancer of in Timor Leste which is 250% higher than Indonesia; and the 1300% difference in testicular cancer between Mali and Mauritania. The IARC approach has a substantial subjective component in the choice of which modeling strategy to use and does not provide any estimate of uncertainty intervals. Empirical assessment of the validity of the GLOBOCAN methods such as through cross-validation would help to understand the strength of their approach.

Understanding causes of death begins with the assessment of all-cause mortality. There are some notable differences between our assessment of global age-specific deaths and those produced by the United Nations Population Division in their World Population Prospects 2012 revision (WPP2012). For the three time periods (1995-2000, 2000-2005, and 2005-2010) as defined in WPP2012, the global total numbers of deaths are around 2.4% to 3.6% (6.1 million to 9.1 million) higher than estimated by the current study. These differentials translate into differences of 7.8 million of deaths for the five year period between 2005 and 2010. With close examination, the difference is more pronounced in younger age groups. For the period 2005-2010, the estimated under-five deaths from WPP2012 are 10.7% higher [or 3.9 million more in death numbers] than GBD 2013. WPP2012's estimates are also higher than the current global under-five death estimates from UNICEF; part of this difference may be traced to differences in the timing of different agencies releases of estimates. In relative terms, the biggest difference can be found in the adolescent age group (ages 5-14). For the years between 2005 and 2010, the estimated deaths in the adolescent age group from WPP2012 are 45.1% higher than the current study even though the absolute difference is about 2.2 million for a five-year period, less than 1% (2.17 million/264.7 million) of the total deaths for the same time period. Much higher levels of heterogeneity exist for differences when we look at the differences at the GBD regional level. For 2005-2010, the relative difference between WPP2012 and GBD 2013 ranges from 26.7% [122.8 thousand] lower in WPP2012 in Oceania to 36.0% [1.9 million] higher in WPP2012 in central sub-Saharan Africa. WPP2012 tends to have much higher estimates of adolescent mortality estimates for all regions in sub-Saharan Africa, Andean Latin America, north Africa and Middle East, and southeast Asia. Overall, we find more differences in estimates for sub-Saharan Africa across all age group in both relative and absolute terms. Such discrepancy in estimated adolescent deaths originates from different assessments of child mortality rates and the difference in model life table systems, both of which utilize child mortality rate to generate age-specific mortality rates. Recent studies have pointed out the importance of estimating mortality for the adolescent age group.[117–119] As part of the background research for the GBD 2013, we have directly examined the DHS complete birth history data for age-groups 5-9 and 10-14 and compared this in countries with near-complete VR or sample registration systems such as India. In addition, we also systematically examined estimates of adolescent mortality from sites of the health and demographic surveillance systems, a network known as INDEPTH. When we look at the ratio of 5q5 [probability of death from birth age 5 to age 10] and 5q10 [probability of death from age 10 to age 15] to U5MR, conflicting pictures arise: our GBD2013 estimates are sometimes higher than one source and lower than the other. Further analysis is warranted to validate our approaches in estimating adolescent mortality in low and middle income countries without working vital registration system. In addition, efforts also need to be spent on improving both data collection and method development in better estimating mortality for the adolescent age group.

As in the GBD 2010, we find notable differences in our analysis of causes of child death compared with those produced by the Child Health Epidemiology Reference Group (CHERG) which are highlighted in table 7. Our estimates of lower respiratory infections (pneumonia) are 112 thousand lower in neonates, and 299 thousand lower in children aged one to 59 months for the year 2010. Given the complexity of both the GBD and CHERG approaches, it is difficult to isolate the reason for the differences. One important difference may be the universe of studies used: we included 5,031 site-years of vital registration (VR) and 356 of verbal autopsy (VA) compared to 578 and 192 for CHERG. Our modeling strategy is founded on modeling each individual cause separately using what we view as the most

appropriate method for each cause and then combining the different cause estimates into an overall assessment consistent with all-cause mortality using the CoDCorrect algorithm. CHERG uses separate modeling strategies for HIV/AIDS, measles, pertussis, and malaria outside of Africa, and four different models for the remainder of the child causes: pneumonia, diarrhoea, sepsis, meningitis, preterm birth complications, intrapartum-related complications, congenital anomalies, tetanus, injuries, and other. Separate logistic models, each with subtly incomparable cause lists, were employed for neonates and children older than one month, for low mortality countries excluding China, for high mortality countries excluding India, a separate model using only data for India, and a completely different modelling strategy for China. This partition of the world into separate models has not been justified statistically; for example, they have not demonstrated statistically different relationships with covariates for their four sets of models. Additionally, post-estimation adjustments were applied to pneumonia, meningitis, and malaria to account for intervention effectiveness, pneumonia, sepsis, meningitis, and tetanus to account for the reliance on a combined 'severe infection' cause in the primary model, and diarrhoea, neonatal sepsis, and sudden infant death syndrome in China to account for studies which report few causes. We have used a more empirical approach. In our assessment, we quantify both the root-mean squared error and validity of the uncertainty intervals through a cross-validation strategy; CHERG has not to date reported any cross-validation results. Given the hypothesis that there may be different relationships between covariates such as access to clean water or sanitation and diarrhoeal mortality in different parts of the world, we undertook a sensitivity analysis where we excluded vital registration data from developed regions from the models for lower respiratory infections and diarrhoea; We have not found substantial differences in estimated global cause of death patterns in these cases. Further, in the CHERG cause of death, neonatal causes are assumed to not cause deaths after one month although high quality vital registration systems routinely report deaths from these causes that extend into the second month of life.

Methods challenges and limitations

In the GBD 2013, a number of important clinical pathways to death such as heart failure, sepsis, fungal infection, and acute kidney injury do not appear in the cause list. These clinical entities following the underlying cause construct of the ICD are treated as garbage codes and redistributed to the likely underlying cause. While this is consistent with the idea of assigning each death uniquely to the underlying cause, it masks in the GBD results important endpoints for clinical service delivery. For example, fungi infect billions of people every year. Most are "relatively" minor infections, but potentially millions contract invasive fungal diseases[120] that can be important pathways to death. Similar assessments can be made for sepsis, acute kidney injury and heart failure. In future iterations of the GBD, we will seek to quantify mortality that occurs through these intermediate causes. Such intermediate cause estimation cannot be presented in the same causes lists as underlying causes of death but can provide supplemental and important information on these real clinical entities that would otherwise go unrecognized in global epidemiology.

Even in high-income countries with complete vital registration systems, our results can and do differ from official statistics.[121] This is in a large part due to the GBD emphasis on enhancing comparability through the redistribution of deaths assigned to garbage codes. Careful examination of country-specific cause of death data reveals substantial national variation in coding practice. In general, we have used global or regional algorithms for redistributing deaths assigned to garbage codes. This is a

comparatively coarse approach that does not capture important local variation in certification practice or timing of implementation of coding rules. The GBD 2013 represents the most detailed effort to date to try and systematically deal with garbage code redistribution. Some changes in garbage code redistribution such as the treatment of ill-defined cancers or heart failure using statistical approaches have altered GBD 2013 results compared to GBD 2010. We believe that the GBD results including the fraction of deaths assigned to different types of garbage codes can be a useful input into national statistical authorities' efforts to improve medical certification of causes of death. We also believe that through the extensive network of GBD collaborators, we can move in future research to more country-specific redistribution algorithms. To ensure comparability, however, it will be important to ground these national variations in a sound statistical approach and theory of measurement.

A study of this scope has many important limitations; here we highlight some major issues. First, the greatest limitation is the quality of the underlying medical certification of causes of death and verbal autopsy data that are the primary input into the analysis. Various studies have highlighted that even medical certification of causes of death has limitations which is highlighted by the need for garbage code redistribution.[104,122,123] Moreover, verbal autopsy data vary substantially in terms of the instrument used and the training given to physicians assigning causes of death from the verbal autopsies. There remains considerable potential for lack of comparability of cause of death data across countries and for our estimates based on these data given these issues. Second, we have not incorporated uncertainty from garbage code redistribution into our estimation of uncertainty intervals. Propagating uncertainty in the redistribution algorithms into the CODEm models will require revision of the modeling strategy or an enormous increase in computational time. As evidenced by the change for some causes compared to the GBD 2010 due to changes in redistribution derived from statistical methods, this is an important area for future research. Third, the major expansion of data on China that is reflected in this study and the associated changes in the estimates for some but not all causes, highlights that uncertainty intervals cannot take into account data that have not been included in the analysis. Fourth, for some causes, CODEm produces larger uncertainty intervals in high-income countries than may be expected. This is largely due to heterogeneity across high-income countries for a cause that cannot be explained by the models. This is more notable for some causes such as diabetes where there are reasons to believe that marked variation remains in certification practice across high-income countries.[124] Given that diabetes or more generally elevated fasting plasma glucose is a risk factor for macro-vascular outcomes, differences in how physicians interpret the meaning of underlying cause could explain such national variation in practice. In the GBD, the full consequences of elevated fasting plasma glucose are captured in the risk factor assessment[8]; diabetes deaths in this analysis are only those where it is assessed on the death certificate to be the underlying cause. Fifth, although there is special effort in the GBD to enhance the comparability of cause of death data overtime through mapping variants of the ICD and garbage-code redistribution, our time trends may be affected in some cases in changes in diagnostic technology. Some causes such as some cancers may have been less likely to have been diagnosed in the 1980s and 1990s with less widespread use of imaging and other diagnostic steps. Sixth, for chronic kidney disease, the breakdown into deaths from diabetes, hypertension, acute glomerulonephritis, and other depend on both detailed cause of death data and renal registry data. In clinical practice, in patients with both hypertension and diabetes, assigning CKD to a particular cause may be difficult. Seventh, for natural history models, most notably for HIV/AIDS, changes in parameter assumptions such as the death rate on or off ART, can have a profound effect on estimated mortality. We believe that

progressive revision of these models improves the estimates but nevertheless it is hard to validate natural history models. For CODEm, we are able to quantify using the cross-validation strategy model performance but this is not possible with the natural history models. Eighth, a strength of the GBD approach is that all estimates of cause-specific mortality must sum to all-cause mortality in a country-age-sex-year group. One implication of this, however, is that estimates for a specific cause are influenced by the estimates for all other causes. Given the CoDCorrect algorithm, causes of death such as malaria that have very wide uncertainty intervals are particularly influenced by the estimates of other causes. Ninth, models used to generate estimates of all-cause mortality and cause-specific mortality make use of an extensive list of covariates. Uncertainty in these covariates such as uncertainty in GDP per capita is not routinely quantified but nevertheless may be substantial. We have not been able to propagate uncertainty in the independent variables used in the modeling stages into the final results. 95% uncertainty intervals may, therefore, be under-estimated. Where we have tested in a few cases the effect of propagating uncertainty in the independent variables in the case of the HIV crude death rate, the changes in the uncertainty intervals, however, have been relatively minor. Tenth, GBD 2013 has made extraordinary efforts in propagating uncertainty throughout our entirely all-cause mortality estimation process, which is a yet-to-be common practice in modern demographic research. However, uncertainty in covariates used in the first stage model of child and adult mortality rate analysis is not included due to the complexity of added computation and the fact that these covariates have minor impact on our final estimates as indicated by our preliminary testing. Lastly, empirical age patterns of mortality, which are vital in the estimation of mortality for many low- and middle-income countries, mostly come from developed countries with great vital registration systems and some developing countries in the most recent time period. Countries in the Sub-Saharan African region are least represented in our empirical database of age pattern of mortality (as shown in appendix table 4 pp 81-89). while propagating uncertainty from U5MR and adult mortality rates, two key entry parameters for our new model life table system, and uncertainty in the standard life table generation process has given our death estimates in the aforementioned SSA countries considerable uncertainty, accurate documentation of age pattern of mortality in these countries are key in producing best all-cause mortality estimates in the future.

Conclusion

Global public policy to reduce premature death in populations requires a detailed, up to date and accurate understanding of progress (or lack thereof) with disease and injury control strategies. This understanding applies not just to diseases that have been the focus of global public health efforts for the past few decades, but increasingly, as this encyclopedic accounting of epidemiological change worldwide has shown, for newly recognized contributors to global health trends. Through the process of developing annual updates, the GBD is transforming into a collective approach to global health surveillance. Ideally, it will aggregate data from all available sources and provide a coherent view of health levels and trends that is timely, valid and local. To fully achieve the vision of a collective process of global health surveillance, more emphasis in future efforts will need to be placed on shortening the time lag between data collection, reporting, and inclusion in the GBD. Public policy in countries will be that much better informed if such periodic global assessments are accompanied by progressively decreasing uncertainty around the estimates. That is less likely to occur because of further methodological advances in diseases modelling and data synthesis, but much more as a result of greater

investment and awareness among countries and donors alike of the need to strengthen vital health information systems.

Global collective action to reduce mortality from major communicable diseases such as diarrhoea, measles, tetanus, tuberculosis, and, more recently, HIV/AIDS and malaria, is working, but will require continued intervention efforts and resources and will likely be even more responsive if periodic assessments such as that reported here are available, and used. While progress is being made in controlling several major non-communicable diseases of global concern, others have been largely neglected but are rising in importance, particularly drug use disorders, cirrhosis, diabetes, and chronic kidney disease. Greater prominence to reducing disease burden from these diseases, as well as continuing priority for injury control, is strongly suggested by this analysis. The findings on trends in mortality from diseases at the global, regional and national level should provide an important baseline for discussions about the next generation of health goals and targets to come after the Millennium Development Goals.

Research in context panel

We systematically searched all public sources and compilations of mortality data such as the WHO Mortality database, national statistical websites, cancer registries, published and unpublished verbal autopsy studies to identify data containing any information about population level mortality and cause of death patterns, including unpublished studies uncovered through our national expert networks. All data were screened for quality and adjustments were made for known biases such as changes in the ICD revision used for coding, under-registration, and national variation in certification practice. After all adjustments were made, 0.9% of the data were excluded because of remaining issues of quality. A range of modeling strategies were used to make estimates for each cause taking into account country-years with no data and conflicting data for a country-age-sex-cause-year.

This study provides the most recent (2013) comprehensive global description of mortality levels and patterns worldwide, and provides the evidence to assess progress with global development goals, including NCD control, and priorities for further global health and development debates. Because the study provides a complete re-analysis of the time trend for each cause from 1990 to 2013, it supersedes the results of the GBD 2010 study. This is the first-time that country-specific results for all 188 countries over 50 thousand population have been published in a comprehensive manner. Country-specific data provide the opportunity to also examine the extent to which there is epidemiological convergence across countries.

Figures and Tables

Figure 1. Flowchart of all-cause and cause-specific mortality estimation
ICD = International Classification of Diseases, BTL = Basic tabulation list, MI ratio = mortality-to-incidence ratio, CODEm = Cause of Death Ensemble model, CoDcorrect = CoDCorrect algorithm, YLLs = years of life lost

Figure 2. Map of site-years of any cause of death data by country, 1980 - 2013

Figure 3. Total garbage and non-garbage coded deaths from vital registration and verbal autopsy sources, 1990-2013

Figure 4. Annual change in global life expectancy at birth for males and females by year, 1990-2013

Figure 5. Distribution of global deaths by age and GBD super region in 1990 and 2013

Figure 6. Change in age-specific population-weighted Gini coefficient vs. relative change in mortality rate from 1990 to 2013
Solid points show age-groups where the mean absolute difference between countries (population-weighted) has increased and hollow points where mean absolute difference has decreased.

Figure 7. Change in life expectancy at birth by GBD region and cause group from 1990 to 2013
Changes in life expectancy due to specific causes were decomposed from the difference between all-cause life tables and cause-deleted life tables (mortality set to zero for a specific cause). Because all changes in life expectancy are based on cross-sectional life tables, the cause-specific changes add up to the total change in life-expectancy.

War+Disaster = Forces of nature, war, and legal intervention, Intent Inj = Self-harm and interpersonal violence, Unint Inj = Unintentional injuries, Tran Inj = Transport injuries, Oth NCD = Other non-communicable diseases, MSK = Musculoskeletal disorders, Diab+Urog+Hem = Diabetes, urogenital, blood, and endocrine diseases, Mental = Mental and behavioural disorders, Neuro = Neurological disorders, Digestive = Digestive diseases, Cirrhosis = Cirrhosis, Chr Resp = Chronic respiratory diseases, CVD = Cardiovascular diseases, Neoplasms = Neoplasms, Oth Group I = Other communicable, maternal, neonatal, and nutritional diseases, Nutr Def = Nutritional deficiencies, Neonatal = Neonatal disorders, Maternal = Maternal disorders, NTD+Malaria = Neglected tropical diseases and malaria, Diar+LRI+Oth = Diarrhoea, lower respiratory infections, and other common infectious diseases, HIV+TB = HIV/AIDS and tuberculosis

Figure 8. Percent change in age-standardized death rate and absolute change in mean absolute difference and Gini coefficient by cause group from 1990 to 2013

Figure 9. Child death rates in ages <1 month and 1-59 months by region for major causes in 2013
The set of causes is mutually exclusive and collectively exhaustive. A) under one month per person-year of exposure; B) between 1 and 59 months per person-year of exposure.

Figure 10. Top 50 causes of global YLLs in 1990 and 2013 with median % change, 1990-2013
95% uncertainty intervals for ranks and percent change are shown in brackets.

Figure 11. Global all ages YLL rate 1990 – 2013 for major selected causes

Figure 12. Probability of death from birth to exact age 15 (15q0) by country and sex for major causes in 2013
The set of causes is mutually exclusive and collectively exhaustive.*

Figure 13. Probability of death from exact age 15 to exact age 50 (35q15) by country and sex for major causes in 2013

The set of causes is mutually exclusive and collectively exhaustive.*

Figure 14. Probability of death from exact age 50 to exact age 75 (25q50) by country and sex for major causes in 2013
The set of causes is mutually exclusive and collectively exhaustive.*

*Cause legend for Figures 12 - 14

War+Disaster = Forces of nature, war, and legal intervention
Violence = Interpersonal violence
Self-harm = Self-harm
Poison = Poisonings
Drown = Drowning
Fall = Falls
Fire = Fire, heat and hot substances
Transport = Transport injuries
Congenital = Congenital anomalies
CKD = Chronic kidney diseases
Diabetes = Diabetes mellitus
Alzh = Alzheimer's disease and other dementias
Digestive = Digestive diseases (except cirrhosis)
Cirrhosis = Cirrhosis of the liver
Chronic Resp = Chronic respiratory diseases
Stroke = Cerebrovascular disease
IHD = Ischemic heart disease
Colorectal = Colon and rectum cancers
Prostate = Prostate cancer
Cervix = Cervical cancer
Breast = Breast cancer
Lung = Trachea, bronchus, and lung cancers
Liver = Liver cancer
Stomach = Stomach cancer
Nutr Def = Nutritional deficiencies
Neonatal = Neonatal disorders
Maternal = Maternal disorders
Malaria = Malaria
LRI = Lower respiratory infections
Diarrhea = Diarrheal diseases
HIV = HIV/AIDS
TB = Tuberculosis
Cardio & Circ = Cardiovascular and circulatory diseases
Preterm = Preterm birth complications
Hemog = Hemoglobinopathies and hemolytic anemias

Intestinal = Intestinal infectious diseases
Whooping = Whooping cough
N Oth = Other neonatal disorders
Suffocation = Unintentional suffocation
Measles = Measles
N Hemo = Hemolytic disease in fetus and newborn and other neonatal jaundice
SIDS = Sudden infant death syndrome
Meningitis = Meningitis
Tetanus = Tetanus
Leukemia = Leukemia
Brain = Brain and nervous system cancers
Syphilis = Syphilis
F Body = Foreign body
N Sepsis = Sepsis and other infectious disorders of the newborn baby
Intent Inj = Self-harm and interpersonal violence
N Enceph = Neonatal encephalopathy (birth asphyxia and birth trauma)

Figure 15. Top 10 causes of YLLs for both sexes combined by location in 2013
To aid in identification of local variation, the top 15 global causes of YLLs are color-coded.

Table 1: Covariates used in the GBD 2013

Table 2. Number of site-years in database by source type with absolute change from GBD2010

Table 3. Global deaths for all ages and both sexes combined and age-standardized death rates by cause in 1990 and 2013 with median percent change 1990-2013
95% uncertainty intervals are shown in brackets.

Table 4. Demographic and epidemiological shifts in global cause-specific mortality, 1990 -2013

Table 5. Global child deaths in ages <1 month and 1-59 months for select causes in 1990 and 2013 with median percent change, 1990-2013
95% uncertainty intervals are shown in brackets.

Table 6. Counterfactual deaths (in thousands) and population attributable fractions for diarrhoea and lower respiratory infection pathogens for under-five and all ages in 1990 and 2013 with annual percent change 1990-2013
No identified etiology = Number or proportion of diarrhea/LRI deaths attributable to any diarrhea/LRI pathogens (listed in the table). Because of interaction between pathogens (especially for LRI), the value is the minimum amount of unexplained deaths.

Table 7. Comparison of GBD and CHERG estimated child deaths in ages <1 month and 1-59 months for select causes in 2010 (in thousands)

95% uncertainty intervals are shown in brackets.

Appendix Figures and Tables

Figure 1: Number of all-cause mortality data sources by country, 1950 - 2013

Figure 2: Empirical weights by region

Figure 3: Relative risks for generalized epidemic

Figure 4: Relative error in estimated probability of death

Figure 5: Comparison of old and new population age standard

Figure 6a: Change in Mean Age at Death for Both Sexes Combined, 1990 to 2013

Figure 6b: Change in Mean Age at Death for Females, 1990 to 2013

Figure 6c: Change in Mean Age at Death for Males, 1990 to 2013

Figure 7: Change in country-specific life expectancy at birth for male/female pairs from 1990 - 2013

Figure 8. Site years of vital registration by ICD type for 1980 – 2013

Figure 9: Comparisons of proportionality redistribution of C14 (or 149) on three related cancers by age in global level

Figure 10: Comparisons of assigned fraction of C14 (or 149) on nasopharynx cancer by regions for all ages

Figure 11: Comparisons of assigned fraction of C14 (or 149) on oral cavity and lip cancer by regions for all ages

Figure 12: Comparisons of assigned fraction of Y20 "Hanging, strangulation and suffocation, undetermined intent" on related injuries by ages in global level

Figure 13: Comparisons of assigned fraction of I64 "Stroke, not specified as hemorrhage or infarction" on related injuries by ages in global level

Table 1: Number of years with data points by country and decade

Table 2: Data source list of child and adult mortality data sources used in the GBD 2013

Table 3: Variance from the first and second stage models

Table 4: Source for empirical life tables used in GBD 2013 by sex

Table 5: Model estimates by age and sex

Table 6: New world population age-standard

Table 7: Regional deaths in thousands with 95% uncertainty by age and sex in 1990, 2000, 2013

Table 8: Mean age at death by country and year for both sexes combined

Table 9: Under-five mortality (5q0), adult mortality (45q15), and life expectancy at birth by country and sex in 1990 and 2013

Table 10: Ages 15-49 mortality (35q15) and ages 50-74 mortality (25q50) by country and sex in 1990 and 2013

Table 11: Total number of site years by source type and cause for 2013 excluding studies on LRI and diarrhea etiologies

Table 12: Total number of site years by cause by region for 2013 excluding studies on LRI and diarrhea etiologies

Table 13: Source list by country and site, source type, study site, time period, age range, and deaths excluding sources on LRI and diarrhea etiologies

Table 14: List of International Classification of Diseases (ICD) codes mapped to the Global Burden of Disease cause list for causes of death

Table 15: Disagregation of ICD9 Basic Tabulation: Example B14.9 "Remainder of B14: Malignant neoplasm of lymphatic and haemopoietic tissue" in females

Table 16: Cause fractions before and after redistribution at the global and super-region level for 2008 excluding studies on LRI and diarrhea etiologies

Table 17: GBD 2010 and GBD 2013 comparison of cause fractions before and after redistribution for 1995 ICD9 vital registration excluding studies on LRI and diarrhea etiologies

Table 18: GBD 2010 and GBD 2013 comparison of cause fractions before and after redistribution for 2008 ICD10 vital registration excluding studies on LRI and diarrhea etiologies

Table 19: Modeling strategy and CoDCorrect level by cause of death

Table 20: Causes of death for which the modelling strategy changed from GBD 2010 to GBD 2013

Table 21: CODEm predictive validity results by cause, sex, age, and location

Table 22: CODEm covariates used, level of covariate, and expected direction of covariate by cause, sex, age, and location

Table 23: Comparison of GBD 2010 and GBD 2013 covariates used in causes of death modeling

Table 24: Percent change for level 1 CoDCorrect causes in 2013

Table 25: Global deaths by age, sex, and cause in 1990

Table 26: Global deaths by age, sex, and cause in 2013

Table 27: Global death rates (per 100k) by age, sex, and cause in 1990

Table 28: Global death rates (per 100k) by age, sex, and cause in 2013

Table 29: Global YLLS by age, sex, and cause in 1990

Table 30: Global YLLs by age, sex, and cause in 2013

Table 31: Country deaths by age, sex, and cause in 2013

Table 32: Data citation list by country for causes of death and mortality data excluding studies on LRI and diarrhea etiologies

Table 33: Data citation list by country for LRI and diarrhea etiologies

References

1 Institute for Health Metrics and Evaluation. Protocol, GBD 2013: global burden of diseases, injuries, and risk factors. 2013 http://www.healthdata.org/gbd/about/protocol.

2 Wang H, Dwyer-Lindgren L, Lofgren KT, *et al.* Age-specific and sex-specific mortality in 187 countries, 1970–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 2012; **380**: 2071–94.

3 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. *The Lancet* 2012; **380**: 2095–128.

4 Salomon JA, Wang H, Freeman MK, *et al.* Healthy life expectancy for 187 countries, 1990–2010: a systematic analysis for the Global Burden Disease Study 2010. *The Lancet* 2012; **380**: 2144–62.

5 Salomon JA, Vos T, Hogan DR, *et al.* Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2129–43.

6 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. *The Lancet* 2012; **380**: 2163–96.

7 Murray CJL, Vos T, Lozano R, *et al.* Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 2012; **380**: 2197–223.

8 Lim SS, Vos T, Flaxman AD, *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet* 2012; **380**: 2224–60.

9 Lozano R, Gómez-Dantés H, Garrido-Latorre F, *et al.* [Burden of disease, injuries, risk factors and challenges for the health system in Mexico]. *Salud Pública México* 2013; **55**: 580–94.

10 Yang G, Wang Y, Zeng Y, *et al.* Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010. *The Lancet* 2013; **381**: 1987–2015.

11 Murray C, Abraham J, Ali M. The state of US health, 1990-2010: Burden of diseases, injuries, and risk factors. *JAMA* 2013; **310**: 591–606.

12 Murray CJ, Richards MA, Newton JN, *et al.* UK health performance: findings of the Global Burden of Disease Study 2010. *The Lancet* 2013; **381**: 997–1020.

13 Forouzanfar MH, Sepanlou SG, Shahraz S, *et al.* Evaluating causes of death and morbidity in Iran, global burden of diseases, injuries, and risk factors study 2010. *Arch Iran Med* 2014; **17**: 304–20.

14 Naghavi M, Shahraz S, Sepanlou SG, *et al.* Health transition in Iran toward chronic diseases based on results of Global Burden of Disease 2010. *Arch Iran Med* 2014; **17**: 321–35.

15 Shahraz S, Forouzanfar MH, Sepanlou SG, *et al.* Population Health and Burden of Disease Profile of Iran among 20 Countries in the Region: From Afghanistan to Qatar and Lebanon. *Arch Iran Med* 2014; **17**: 336–42.

16 USAID. Global Health Programs: Progress Report to Congress FY 2012. Washington, DC, 2013.

17 WHO. Roadmap for Childhood Tuberculosis. 2013. http://apps.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf. .

18 UNAIDS. 2011-2015 Strategy: Getting to Zero. Joint United Nations Programme on HIV/AIDS, 2010. http://www.unaids.org/en/media/ unaids/contentassets/documents/unaidspublication/2010/JC2034_ UNAIDS_Strategy_en.pdf. .

19 Treatment Action Group (TAG). The Zero Declaration. July 22, 2012. New York, NY. http://www.treatmentactiongroup.org/tb/advocacy/zero-declaration. .

20 Stop TB. Partnership. No More Crying, No More Dying. Towards Zero TB Deaths In Children., WHO, 2012 http://www.stoptb.org/assets/documents/news/ChildhoodTB_report_singles.pdf. .

21 South Africa Info Reporter. South Africa's HIV/Aids battle plan. SouthAfrica.info. 2012. http://www.southafrica.info/about/health/aids-prevention.htm#.UxZ1nfldXg9. .

22 Ki-moon B. Secretary-General's message on World Malaria Day. un.org. 2011. http://www.un.org/sg/statements/?nid=5219. .

23 Department for International Development. UKAID. Towards zero infections: The UK's position paper on HIV in the developing world. 2011 https://www.gov.uk/government/uploads/system/uploads/ attachment_data/file/67523/twds-zero-infs-pos-paper-hiv-dev-wrld.pdf. .

24 The World We Want. Health in the Post-2015 Agenda: Report of the Global Thematic Consultation on Health. 2013 http://www.worldwewant2015.org/health.

25 WHO. Positioning Health in the Post-2015: WHO discussion paper. Geneva, Switzerland: World Health Organization, 2012 http://www.who.int/topics/millennium_development_goals/post2015/WHOdiscussionpaper_October2012.pdf.

26 Jamison DT, Summers LH, Alleyne G, *et al.* Global health 2035: a world converging within a generation. *The Lancet* 2013; **382**: 1898–955.

27 Atun R, Jaffar S, Nishtar S, *et al.* Improving responsiveness of health systems to non-communicable diseases. *Lancet* 2013; **381**: 690–7.

28 Institute for Health Metrics and Evaluation. The Global Burden of Disease: generating evidence, guiding policy. Seattle, WA: IHME, 2013.

29 James SL, Gubbins P, Murray CJ, Gakidou E. Developing a comprehensive time series of GDP per capita for 210 countries from 1950 to 2015. *Popul Health Metr* 2012; **10**: 12.

30 Gakidou E, Cowling K, Lozano R, Murray CJ. Increased educational attainment and its effect on child mortality in 175 countries between 1970 and 2009: a systematic analysis. *The Lancet* 2010; **376**: 959–74.

31 Ng M, Fleming T, Robinson M, *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2014; published online May. DOI:10.1016/S0140-6736(14)60460-8.

32 Ng M, Freeman MK, Fleming TD, *et al.* Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA J Am Med Assoc* 2014; **311**: 183–92.

33 Wang H, Liddell CA, Coates MM, *et al.* Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*.

34 Murray CJL, Rajaratnam JK, Marcus J, Laakso T, Lopez AD. What can we conclude from death registration? Improved methods for evaluating completeness. *PLoS Med* 2010; **7**: e1000262.

35 Obermeyer Z, Rajaratnam JK, Park CH, *et al.* Measuring adult mortality using sibling survival: a new analytical method and new results for 44 countries, 1974–2006. *PLoS Med* 2010; **7**: e1000260.

36 Kannisto V. Development of oldest-old mortality, 1950-1990: evidence from 28 developed countries. Odense University Press, 1994.

37 Gompertz B. On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. *Philos Trans R Soc Lond* 1825; **115**: 513–83.

38 Murray CJL. Global, regional and national incidence and death for HIV, tuberculosis and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. In press.

39 Zellner A. An efficient method of estimating seemingly unrelated regressions and tests for aggregation bias. *J Am Stat Assoc* 1962; **57**: 348–68.

40 UNAIDS. Methodology – Understanding the HIV estimates. Strategic Information and Monitoring Division, 2013 http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/20131118_Methodology.pdf.

41 Department of Peace and Conflict Research. Uppsala Conflict Data Program. Uppsala, Sweden. Uppsala Universitet. http://www.pcr.uu.se/research/UCDP/. .

42 The International Institute For Strategic Studies. Armed Conflict Database. London, United Kingdom. https://acd.iiss.org/. .

43 WHO. WHO Mortality Database. http://www.who.int/healthinfo/cod/en/ (accessed May 5, 2014).

44 Centre for Research on the Epidemiology of Disasters (CRED), Office of US Foreign Disaster Assistance (OFDA). EM-DAT:The OFDA/CRED international disaster database. Brussels, Belgium, Université Catholique de Louvain. http://www.emdat.be/database. .

45 United Nations Department of Economics and Social Affairs Population Division. World Population Prospects: The 2012 Revision. http://esa.un.org/unpd/wpp/Documentation/publications.htm.

46 Wheldon MC, Raftery AE, Clark SJ, Gerland P. Reconstructing Past Populations With Uncertainty From Fragmentary Data. *J Am Stat Assoc* 2013; **108**: 96–110.

47 Murray CJ, Lozano R, Flaxman AD, *et al.* Using verbal autopsy to measure causes of death: the comparative performance of existing methods. *BMC Med* 2014; **12**: 5.

48 Forman D, Brewster D, Gombe Mbalawa C, *et al.* Cancer incidence in five continents volume X. WHO: International Agency for Reserach on Cancer, 2013 http://ci5.iarc.fr/CI5-X/ci5-X.htm (accessed April 24, 2014).

49 Ahern RM, Lozano R, Naghavi M, Foreman K, Gakidou E, Murray CJ. Improving the public health utility of global cardiovascular mortality data: the rise of ischemic heart disease. *Popul Health Metr* 2011; **9**: 8.

50 WHO. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010. Geneva, Switzerland http://apps.who.int/classifications/icd10/browse/2010/en#/X59 (accessed May 5, 2014).

51 WHO. WHO Evidence Review Group: Malaria Burden Estimation. Report on the Second Meeting, Geneva, Switzerland, 2013 http://www.who.int/malaria/mpac/malaria_burden_estimates_report.pdf (accessed May 4, 2014).

52 Foreman KJ, Lozano R, Lopez AD, Murray CJ. Modeling causes of death: an integrated approach using CODEm. *Popul Health Metr* 2012; **10**: 1.

53 Ortblad KF, Lozano R, Murray CJL. The burden of HIV: insights from the Global Burden of Disease Study 2010. *AIDS* 2013; **27**: 2003–17.

54 Flaxman A, Vos T, Murray C. An Integrative Metaregression Framework for Descriptive Epidemiology. Seattle: University of Washington Press, in press.

55 Blackwelder WC, Biswas K, Wu Y, *et al.* Statistical methods in the Global Enteric Multicenter Study (GEMS). *Clin Infect Dis Off Publ Infect Dis Soc Am* 2012; **55 Suppl 4**: S246–253.

56 Kotloff KL, Nataro JP, Blackwelder WC, *et al.* Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *The Lancet* 2013; **382**: 209–22.

57 Hanley JA. A heuristic approach to the formulas for population attributable fraction. *J Epidemiol Community Health* 2001; **55**: 508–14.

58 Levine MM, Kotloff KL, Nataro JP, Muhsen K. The Global Enteric Multicenter Study (GEMS): impetus, rationale, and genesis. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2012; **55 Suppl 4**: S215–224.

59 Kotila SM, Virolainen A, Snellman M, Ibrahem S, Jalava J, Lyytikäinen O. Incidence, case fatality and genotypes causing Clostridium difficile infections, Finland, 2008. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2011; **17**: 888–93.

60 Klugman KP. Contribution of vaccines to our understanding of pneumococcal disease. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 2790–8.

61 Feikin DR, Scott JAG, Gessner BD. Use of vaccines as probes to define disease burden. *The Lancet* 2014; published online Feb. DOI:10.1016/S0140-6736(13)61682-7.

62 Watt JP, Wolfson LJ, O'Brien KL, *et al.* Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. *The Lancet* 2009; **374**: 903–11.

63 O'Brien KL, Wolfson LJ, Watt JP, *et al.* Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *The Lancet* 2009; **374**: 893–902.

64 Baqui AH, El Arifeen S, Saha SK, *et al.* Effectiveness of Haemophilus influenzae type B conjugate vaccine on prevention of pneumonia and meningitis in Bangladeshi children: a case-control study. *Pediatr Infect Dis J* 2007; **26**: 565–71.

65 Gessner BD, Sutanto A, Linehan M, *et al.* Incidences of vaccine-preventable Haemophilus influenzae type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial. *Lancet* 2005; **365**: 43–52.

66 Levine OS, Lagos R, Muñoz A, *et al.* Defining the burden of pneumonia in children preventable by vaccination against Haemophilus influenzae type b. *Pediatr Infect Dis J* 1999; **18**: 1060–4.

67 Mulholland K, Hilton S, Adegbola R, *et al.* Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants. *The Lancet* 1997; **349**: 1191–7.

68 Black SB, Shinefield HR, Ling S, *et al.* Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J* 2002; **21**: 810–5.

69 Cutts FT, Zaman SMA, Enwere G, *et al.* Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *The Lancet* 2005; **365**: 1139–46.

70 Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A Trial of a 9-Valent Pneumococcal Conjugate Vaccine in Children with and Those without HIV Infection. *N Engl J Med* 2003; **349**: 1341–8.

71 Lucero MG, Nohynek H, Williams G, *et al.* Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial. *Pediatr Infect Dis J* 2009; **28**: 455–62.

72 Sigaúque B, Vubil D, Sozinho A, *et al.* Haemophilus influenzae type b disease among children in rural Mozambique: impact of vaccine introduction. *J Pediatr* 2013; **163**: S19–24.

73 Gessner BD, Adegbola RA. The impact of vaccines on pneumonia: key lessons from Haemophilus influenzae type b conjugate vaccines. *Vaccine* 2008; **26 Suppl 2**: B3–8.

74 Simonsen L, Viboud C, Taylor RJ, Miller MA. The Epidemiology of Influenza and Its Control. In: Rappuoli R, Giudice GD, eds. Influenza Vaccines for the Future. Springer Basel, 2011: 27–54.

75 Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. Hospitalizations for Pneumonia after a Decade of Pneumococcal Vaccination. *N Engl J Med* 2013; **369**: 155–63.

76 Gini C. Variabilità e mutabilità, contribrito allo studio delle distribuzioni e delle relazioni statistiche: fascicolo Ier : Introduzione - Indici di variabilità - Indici di mutabilità. Bologne, 1912.

77 Moser K, Shkolnikov V, Leon DA. World mortality 1950-2000: divergence replaces convergence from the late 1980s. *Bull World Health Organ* 2005; **83**: 202–9.

78 Preston S, Heuveline P, Guillot M. Demography: Measuring and Modeling Population Processes, 1 edition. Malden, MA: Wiley-Blackwell, 2000.

79 Beltrán-Sánchez H, Preston SH, Canudas-Romo V. An integrated approach to cause-of-death analysis: cause-deleted life tables and decompositions of life expectancy. *Demogr Res* 2008; **19**: 1323–50.

80 Ahmad O, Boschi-Pinto C, Agresti A. Age Standardization of Rates: A New WHO Standard. WHO, 2001 http://www.who.int/healthinfo/paper31.pdf (accessed May 5, 2014).

81 Mueller Y, Cristofani S, Rodriguez C, *et al.* Integrating mental health into primary care for displaced populations: the experience of Mindanao, Philippines. *Confl Health* 2011; **5**: 3.

82 UNICEF. Committing to Child Survival: A Promise Renewed – Progress Report 2013. New York, N.Y., 2013.

83 USAID. Child survival: call to action. Ending preventable child deaths. Washington D.C.: USAID, 2012.

84 Bustreo F, Say L, Koblinsky M, Pullum TW, Temmerman M, Pablos-Méndez A. Ending preventable maternal deaths: the time is now. *Lancet Glob Health* 2013; **1**: e176–e177.

85 Quah DT. Twin Peaks: growth and convergence in models of distribution dynamics. *Econ J* 1996; **106**: 1045–55.

86 Sala-i-Martin X. The World Distribution of Income: Falling Poverty and … Convergence, Period. *Q J Econ* 2006; **121**: 351–97.

87 Ravallion M. Why don't we see poverty convergence? *Am Econ Rev* 2012; **102**: 504–23.

88 Bloom DE, Canning D. Mortality traps and the dynamics of health transitions. *Proc Natl Acad Sci* 2007; **104**: 16044–9.

89 Clark R. World health inequality: convergence, divergence, and development. *Soc Sci Med* 2011; **72**: 617–24.

90 Wilson C. On the scale of global demographic convergence 1950–2000. *Popul Dev Rev* 2001; **27**: 155–71.

91 Vallin J, Meslé F. Convergences and divergences in mortality. *Demogr Res Spec Collect* 2004; **2**: 11–44.

92 Balabanova D, Mills A, Conteh L, *et al.* Good Health at Low Cost 25 years on: lessons for the future of health systems strengthening. *The Lancet* 2013; **381**: 2118–33.

93 Jamison DT, Breman JG, Measham AR, *et al.*, editors. Disease control priorities in developing countries, 2nd edn. Washington (DC): World Bank, 2006 http://www.ncbi.nlm.nih.gov/books/NBK11728/ (accessed May 6, 2014).

94 Leon DA, Shkolnikov VM, McKee M, Kiryanov N, Andreev E. Alcohol increases circulatory disease mortality in Russia: acute and chronic effects or misattribution of cause? *Int J Epidemiol* 2010; **39**: 1279–90.

95 AIWH: Field B. Rheumatric Heart Disease: all but forgotten in Australia except amoung Aboriginal and Torres Strait Islander people. Australian Insitute of Health and Welfare, 2004 http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442453321.

96 Shakya S, Sharma D, Bhatta Y. Current Scenario of Heart Diseases in Nepal: At a glance. *Nepal Heart J* 2013; **8**. DOI:10.3126/njh.v8i1.8333.

97 Matthews FE, Arthur A, Barnes LE, *et al.* A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *The Lancet* 2013; **382**: 1405–12.

98 United States Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Health Statistics. National Mortality Followback Survey, 1993. Ann Arbor, MI: Inter-university Consortium for Political and Social Research, 2000.

99 Nash TE, Herrington DA, Losonsky GA, Levine MM. Experimental human infections with Giardia lamblia. *J Infect Dis* 1987; **156**: 974–84.

100 Musher DM, Musher BL. Contagious Acute Gastrointestinal Infections. *N Engl J Med* 2004; **351**: 2417–27.

101 Rendtorff RC. The experimental transmission of human intestinal protozoan parasites. II. Giardia lamblia cysts given in capsules. *Am J Hyg* 1954; **59**: 209–20.

102 Yoder J, Harral C, Beach M, Division of Foodborne, Waterborne, and Environmental Diseases (proposed), National Center for Emerging and Zoonotic Infectious Diseases (proposed), CDC. Giardiasis Surveillance - United States, 2006-2008. Centers for Disease Control, 2010.

103 Laishram S, Kang G, Ajjampur SSR. Giardiasis: a review on assemblage distribution and epidemiology in India. *Indian J Gastroenterol Off J Indian Soc Gastroenterol* 2012; **31**: 3–12.

104 Walker CLF, Rudan I, Liu L, *et al.* Global burden of childhood pneumonia and diarrhoea. *The Lancet* 2013; **381**: 1405–16.

105 Nair H, Nokes DJ, Gessner BD, *et al.* Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *The Lancet* 2010; **375**: 1545–55.

106 Nair H, Brooks WA, Katz M, *et al.* Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *The Lancet* 2011; **378**: 1917–30.

107 Pfizer Inc. Pfizer presents detailed results from landmark community-acquired pneumonia immunization trial in adults (CAPiTA) evaluating efficacy of prevenar 13. New York, NY, 2014 http://www.pfizer.com/news/press-release/press-release-detail/pfizer_presents_detailed_results_from_landmark_community_acquired_pneumonia_immunization_trial_in_adults_capita_evaluating_efficacy_of_prevenar_13.

108 Levine OS, O'Brien KL, Deloria-Knoll M, *et al.* The Pneumonia Etiology Research for Child Health Project: A 21st Century Childhood Pneumonia Etiology Study. *Clin Infect Dis* 2012; **54**: S93–S101.

109 Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: Systematic review. *BMC Public Health* 2007; **7**: 357.

110 Sahloul Z, Coutts A, Fouad FM, *et al.* Health response system for Syria: beyond official narrative. *The Lancet* 2014; **383**: 407.

111 Das S, Kolher RP, Mane BG, Singh JPN, Singh AP. Chikungunya epidemic: global and Indian scenario. *J Commun Dis* 2007; **39**: 37–43.

112 Kalantri SP, Joshi R, Riley LW. Chikungunya epidemic: an Indian perspective. *Natl Med J India* 2006; **19**: 315–22.

113 Raheel U, Faheem M, Riaz MN, *et al.* Dengue fever in the Indian Subcontinent: an overview. *J Infect Dev Ctries* 2011; **5**: 239–47.

114 Dhama K, Verma AK, Rajagunalan S, *et al.* Swine flu is back again: a review. *Pak J Biol Sci PJBS* 2012; **15**: 1001–9.

115 International Agency for Research on Cancer. GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. WHO: International Agency for Reserach on Cancer http://globocan.iarc.fr/Default.aspx (accessed May 5, 2014).

116 Forouzanfar MH, Foreman KJ, Delossantos AM, *et al.* Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *The Lancet* 2011; **378**: 1461–84.

117 Hill K, Zimmerman L. Adolescent mortality in low- and middle-income countries. WHO, 2013 http://globalhealth2035.org/sites/default/files/working-papers/adolescent-mortality.pdf (accessed May 5, 2014).

118 Gore FM, Bloem PJ, Patton GC, *et al.* Global burden of disease in young people aged 10–24 years: a systematic analysis. *The Lancet* 2011; **377**: 2093–102.

119 Patton GC, Coffey C, Sawyer SM, *et al.* Global patterns of mortality in young people: a systematic analysis of population health data. *The Lancet* 2009; **374**: 881–92.

120 Brown GD, Denning DW, Levitz SM. Tackling Human Fungal Infections. *Science* 2012; **336**: 647–647.

121 Vangen S, Ellingsen L, Andersgaard AB, *et al.* Maternal deaths in Norway 2005-2009. *Tidsskr Den Nor Laegeforening Tidsskr Prakt Med Ny Raekke* 2014; **134**: 836–9.

122 Roulson J, Benbow EW, Hasleton PS. Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review. *Histopathology* 2005; **47**: 551–9.

123 Sonderegger-Iseli K, Burger S, Muntwyler J, Salomon F. Diagnostic errors in three medical eras: a necropsy study. *The Lancet* 2000; **355**: 2027–31.

124 Murray CJL, Kulkarni SC, Ezzati M. Understanding the Coronary Heart Disease Versus Total Cardiovascular Mortality Paradox A Method to Enhance the Comparability of Cardiovascular Death Statistics in the United States. *Circulation* 2006; **113**: 2071–81.