

Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000



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Summary

Background Information about the distribution of causes of and time trends for child mortality should be periodically updated. We report the latest estimates of causes of child mortality in 2010 with time trends since 2000.

Methods Updated total numbers of deaths in children aged 0–27 days and 1–59 months were applied to the corresponding country-specific distribution of deaths by cause. We did the following to derive the number of deaths in children aged 1–59 months: we used vital registration data for countries with an adequate vital registration system; we applied a multinomial logistic regression model to vital registration data for low-mortality countries without adequate vital registration; we used a similar multinomial logistic regression with verbal autopsy data for high-mortality countries; for India and China, we developed national models. We aggregated country results to generate regional and global estimates.

Findings Of 7·6 million deaths in children younger than 5 years in 2010, 64·0% (4·879 million) were attributable to infectious causes and 40·3% (3·072 million) occurred in neonates. Preterm birth complications (14·1%; 1·078 million, uncertainty range [UR] 0·916–1·325), intrapartum-related complications (9·4%; 0·717 million, 0·610–0·876), and sepsis or meningitis (5·2%; 0·393 million, 0·252–0·552) were the leading causes of neonatal death. In older children, pneumonia (14·1%; 1·071 million, 0·977–1·176), diarrhoea (9·9%; 0·751 million, 0·538–1·031), and malaria (7·4%; 0·564 million, 0·432–0·709) claimed the most lives. Despite tremendous efforts to identify relevant data, the causes of only 2·7% (0·205 million) of deaths in children younger than 5 years were medically certified in 2010. Between 2000 and 2010, the global burden of deaths in children younger than 5 years decreased by 2 million, of which pneumonia, measles, and diarrhoea contributed the most to the overall reduction (0·451 million [0·339–0·547], 0·363 million [0·283–0·419], and 0·359 million [0·215–0·476], respectively). However, only tetanus, measles, AIDS, and malaria (in Africa) decreased at an annual rate sufficient to attain the Millennium Development Goal 4.

Interpretation Child survival strategies should direct resources toward the leading causes of child mortality, with attention focusing on infectious and neonatal causes. More rapid decreases from 2010–15 will need accelerated reduction for the most common causes of death, notably pneumonia and preterm birth complications. Continued efforts to gather high-quality data and enhance estimation methods are essential for the improvement of future estimates.

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Introduction

Globally, 7·6 million children died in 2010 before reaching their fifth birthday.¹ This number decreased from 9·6 million in 2000 and the mortality rate per 1000 livebirths in children younger than 5 years decreased from 73 to 57,¹ showing improved child survival at the global level in the past decade. However, less than 3 years is left to reach the deadline for Millennium Development Goal (MDG) 4—to reduce child mortality by two-thirds between 1990 and 2015.² Only a few countries are on track to achieve this goal, and much acceleration in progress is needed in other countries.^{3,4} Efforts to accelerate progress could be especially efficient if interventions to save lives from important causes of death can be more rapidly scaled up.^{5–7} To guide global and national programmes and

research efforts, information about the distribution of causes of child deaths should be periodically updated. To assess the lasting effects of child health interventions and assist the development of long-term child survival strategies, time trends of child deaths by cause should also be made available with consistent methods. WHO and UNICEF's Child Health Epidemiology Reference Group (CHERG) has published a series of estimates of the distribution of causes of child death during the past decade, during which time estimation methods and the quality and quantity of input data have improved.^{8–12} With additional vital registration data, verbal autopsy data, and improved methods available, we report updated estimates of the distribution of child deaths by cause in 2010 and time trends of child deaths by cause since 2000.

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Methods

Estimation of the number of child deaths

Procedures for the estimation of causes of deaths in children younger than 5 years were based on previous methods (figure 1 and appendix p 3).⁸

See Online for appendix

To obtain the number of deaths in neonates (aged <29 days) and children aged 1–59 months, the country-specific under-5 mortality rates (U5MR) and neonatal mortality rates are needed (appendix p 3). U5MRs were from the latest publication of the UN Interagency Group for Child Mortality Estimation (IGME).¹ The estimation process was largely similar to what had been done previously,¹³ but the estimates were substantially adjusted downward after inclusion of data from new surveys, censuses, and vital registration systems that became available since the previous publication. Neonatal mortality rates were developed by WHO, applying updated methods, which are available elsewhere.¹⁴

Estimated livebirths and population aged <1 years and 1–4 years for 2000–10 were taken from the UN Population Division 2010 revision.¹⁵ We estimated the total number of deaths in neonates and in children younger than 5 years for 2000–10 by applying IGME and WHO estimates for U5MR and neonatal mortality rates to the population of children younger than 5 years and the estimated number of livebirths, respectively. Because of the downward adjustment of the U5MRs, the number of deaths in children younger than 5 years was also reduced in the time series—eg, from the previous estimate of 8·8 million to a new estimate of 7·9 million for 2008. For the few countries where estimated all-age deaths due to conflict and disasters exceeded one per 10000 population,

the estimated number of deaths in children younger than 5 years due to war or disaster was taken from a range of published and unpublished war and disaster mortality databases and added to the estimated deaths for injuries and all causes.^{16–19}

To improve consistency in methods used to estimate causes of deaths in neonates and older children, more than 80% of vital registration coverage with high-quality data was regarded as adequate death registration in both age groups, compared with the cutoff of 80% for neonates and 85% for older children in previous estimates,⁸ which did not take into consideration the quality of data. Vital registration data were regarded as of good quality if the following criteria were met: reasonable distribution of deaths by cause were reported without excessive use of implausible or specific codes, or sufficient details of the coding were provided so that deaths could be grouped into appropriate categories used in the analysis. For countries with adequate death registration, data for causes of child deaths were extracted from the WHO mortality database, adjusted for coverage incompleteness when needed, and grouped according to the standard International Classification of Diseases, 10th revision (ICD-10). For earlier years when ICD-9 codes were used, we applied a mapping system to convert them into ICD-10 codes (appendix p 4). Some neonatal codes were re-assigned from poorly defined codes to more plausible codes.^{8,20} Annual data for years 2000 to the latest available year were included with data closest to the estimating year used. When the latest year available was earlier than 2010, the cause distribution for the latest available year was assumed to apply for the subsequent year or years,

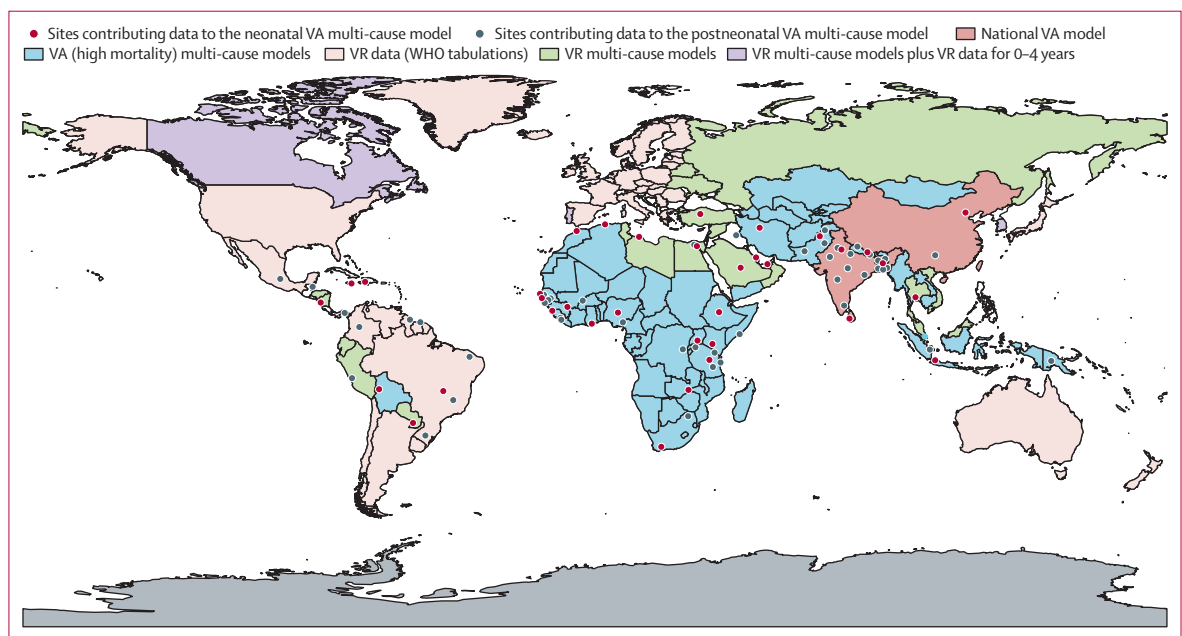


Figure 1: Methods used to estimate causes of death in children younger than 5 years in 2000–10
VA=verbal autopsy, VR=vital registration.

which was then applied to the age-specific total number of child deaths.

For countries with U5MR of 35 or fewer per 1000 livebirths in 2000–10 but without adequate death registration, a previously described multinomial logistic regression model⁸ was revised to estimate the distribution of causes of deaths for neonates and older children separately. The model for neonates was extended to produce separate estimates for pneumonia and sepsis. We selected model covariates using a jackknife procedure for each non-baseline cause of death, choosing the model that minimised the out-of-sample prediction error using the metric of the squared differences between observed and expected deaths divided by expected deaths.

For older children, we revised the original vital-registration-data-based multi-cause model (VRMCM)^{8,10} to include death registration data from 56 countries available in 1998–2010 for a total of 578 datapoints. We used univariate meta-regression methods and multivariate stepwise forward ordinary-least-squares regression models to identify explanatory variables for the log ratio of each cause over pneumonia to be included in the multinomial logistic regression, on the basis of which cause-specific fractions were derived. We combined the model parameters from the multinomial logistic regression with a time-series of national covariates to predict country-specific estimates of the distribution of deaths by cause in 2000–10, which we then applied to the number of deaths (excluding AIDS deaths) in children aged 1–59 months (appendix pp 5–26).

Some countries report mortality data to WHO for children aged 0–59 months without disaggregating cause-of-death data for neonates. For these few countries (of which there were six), deaths by cause in neonates and children aged 1–59 months were imputed from the total number of deaths in children aged 0–59 months with information about the cause-specific ratio of neonatal to postneonatal deaths obtained from the VRMCMs.

For high-mortality countries with a U5MR above 35 per 1000 livebirths in 2000–10 and without adequate death registration, we estimated causes of neonatal deaths using a revised verbal-autopsy-data-based multi-cause model (VAMCM).^{8,11} With new studies identified through an updated systematic review done on Jan 25, 2011, through Feb 8, 2011 (appendix pp 27–28), 89 studies in 34 high-mortality countries that met the inclusion criteria¹¹ were included in the model. We developed a multinomial logistic regression model for six cause categories—complications of preterm birth, intrapartum-related complications (formerly referred to as birth asphyxia), congenital abnormalities, severe infection (including pneumonia, sepsis, meningitis, and tetanus), diarrhoea, and other causes—using a similar approach to model selection to that in the neonatal VRMCM. We then estimated the proportion of severe-infection deaths that were due to pneumonia from 36 studies that presented

separate data for pneumonia deaths (appendix pp 34–35) using a logistic regression model with the percentage of women who were literate, of children born at low birthweight, of births with skilled attendant, and of children protected at birth by tetanus toxoid vaccine as covariates. The number of tetanus deaths was also modelled separately in a single-cause model with the same set of covariates, excluding the percentage of babies born with low birthweight. We applied the resulting cause-specific proportions to the estimated total neonatal deaths in every country and every year.

To estimate causes of death for children aged 1–59 months, we also developed a revised VAMCM.¹⁰ We did an updated systematic review to identify additional verbal autopsy studies published between Jan 1, 2008, and June 1, 2010 (appendix pp 29–33). We also included national and subnational vital registration data from countries with a U5MR greater than 20 per 1000 livebirths to better predict for countries transitioning from a high-mortality profile into a low-mortality profile. Repeated efforts were made to request unpublished study-level information from all corresponding authors and additional data were obtained and included for nine datasets. Two studies with fewer than 25 deaths after exclusion of deaths due to measles, AIDS, and unknown causes were not included. We used 113 datapoints abstracted from 74 studies that used data from 33 countries that met the inclusion criteria.¹⁰ The studies were predominantly done in high-mortality countries with mid-study years between 1980 and 2008.

We grouped causes of death into eight categories, including pneumonia, diarrhoea, meningitis, injury, malaria, congenital abnormalities, causes arising during the perinatal period, and other causes. We grouped deaths due to severe malnutrition as other causes (instead of redistributing them among all infectious causes as done in the previous analysis). A similar set of explanatory variables for the distribution of causes of deaths used previously¹⁰ were also attempted in the model (appendix p 42). We applied stepwise ordinary-least-squares regressions, together with our prior knowledge, to identify explanatory variables with the inclusion criterion set at $p < 0.1$ and exclusion criterion set at $p \geq 0.5$, while considering the within-country clustering. We ran a multinomial logistic regression model to construct the relations between the identified covariates and the cause-specific log ratios with pneumonia as the base category. We entered national-level covariates for 2000–10 (appendix pp 5–7) into the fitted multinomial logistic regression to derive annual national cause-of-death distribution for 79 high-mortality countries. We applied the estimated cause-specific fractions one country at a time to the number of deaths in children aged 1–59 months (excluding measles and AIDS) to obtain the annual cause-specific number of deaths in 2000–10. We further adjusted results for intervention coverage, specifically with pneumonia and

meningitis deaths adjusted for the use and effectiveness of *Haemophilus influenzae* type b vaccine, and malaria deaths adjusted for the coverage and effectiveness of insecticide-treated bednets. Additional details of the postneonatal VAMCM are provided in the appendix (pp 36–42).

We estimated childhood malaria deaths in countries with high malaria transmission using the postneonatal VAMCM described above. For countries in Africa with low malaria transmission that do not have an adequate vital registration system and for those outside Africa, we estimated childhood malaria deaths using a natural history model developed by the WHO malaria programme.²¹ Specifically, we estimated the number of *Plasmodium falciparum* malaria cases on the basis of reported malaria cases after adjusting for report completeness, likelihood of parasite-positivity, and use of health services. Case numbers were multiplied by a fixed case-fatality ratio to derive malaria deaths for each country. We used estimates from the UN Programme on HIV/AIDS (UNAIDS) estimates of country-specific AIDS-related deaths for children for 2000–10 in this analysis.²²

To estimate deaths attributable to measles, we used a new model of measles mortality developed by WHO's Department of Immunization, Vaccines and Biologicals to first estimate country-and-year-specific cases using surveillance data.²³ Cases were then stratified by age and applied to age-specific case-fatality ratios assumed to be constant across time. We aggregated age-specific deaths to derive measles deaths for all children younger than 5 years. The new method took into account herd immunity and produced results that were consistent with previous findings.²⁴ For countries that had measles outbreaks, the measles deaths were split into outbreak deaths and endemic deaths, the latter of which were smoothed with local regression.²⁵ For the ages of 1–59 months, the endemic measles deaths and AIDS deaths were added to the measles-free and AIDS-free all-cause deaths for which the VAMCM-derived cause fractions were applied. We added the measles outbreak deaths back after application of these cause fractions. For countries where the outbreak deaths resulted in an increase in the all-cause deaths by 10% or more, we screened the original survey data to examine whether a real increase in child mortality was indicated for the outbreak year. If survey data were available for the years around the outbreak but there was no evidence of an increased mortality, we truncated the measles outbreak deaths at 10% of the all-cause deaths. Such truncation was necessary in only a few countries, almost all of which are in Africa and all of which occurred in the early 2000s, when more measles deaths were estimated.

Estimation of causes of deaths in India and China

In our previous estimation for India, the distribution of deaths by cause in children younger than 5 years was directly extracted from the Million Death Study,²⁶ with

additional adjustments for selected causes.^{8,26} Because of substantial heterogeneity in coverage of life-saving interventions and disease patterns across states, we developed age-specific subnational models to estimate the causes of child mortality for 35 states in India. To estimate causes of neonatal mortality, we used 37 subnational verbal autopsy studies to predict the cause distribution at the state level using similar methods used for the neonatal VAMCM. For children who died at the age of 1–59 months, we used 45 subnational verbal autopsy studies. We applied a similar analytical framework based on multinomial logistic regression as used for postneonatal VAMCM, using a similar set of covariates at the state level. We specified nine cause categories, including measles plus the eight categories specified in the postneonatal VAMCM for other countries. We then replaced measles deaths with estimates from the WHO's Department of Immunization, Vaccines and Biologicals (described above) and adjusted all-cause fractions to sum to one. We applied the resulting cause-specific proportions to the estimated number of neonatal deaths and deaths of children aged 1–59 months to obtain the state-level number of deaths by cause before combining all these estimates to obtain national estimates.

For China, we applied updated IGME U5MR estimates to the national cause-specific models developed by Rudan and colleagues²⁷ to derive cause-fractions annually in 2000–10. We derived the number of deaths attributable to neonatal tetanus using officially reported mortality rates,²⁸ the quality of which was thought to be sufficient in view of the high institutional delivery rate reported during the past decade.²⁹ Together with cause-specific inputs from UNAIDS and WHO technical programmes for measles and malaria, we adjusted the resulting cause-specific inputs for China to fit the estimated deaths at ages 0–27 days and 1–59 months, respectively.

Model selection and uncertainty estimation

We did cross validation to compare the out-of-sample prediction accuracy between model versions for all multi-cause models. 10% of the study data was reserved, and the remaining 90% was used to build the model. With more than 2000 different random divisions of the data, the average standardised difference between the observed and predicted data was taken as a metric. The best-performing model was chosen as the final model with the smallest absolute prediction error.

We applied bootstrapping instead of the jackknife procedure in this round to construct uncertainty ranges, which allowed narrower but more plausible uncertainty ranges than with use of jackknifing. We estimated the uncertainty bounds for neonates and children aged 1–59 months separately. The bootstrapping procedure sampled with replacement from the distribution of causes of deaths at the model input level. The total uncertainties were conservatively estimated on the basis of combining uncertainties from the VRMCM, the VAMCM, and those estimated by the WHO technical

programmes by adding up the corresponding lower and upper bounds. No uncertainty was assumed for cause fractions directly derived from the vital registration data.

After all estimates were pooled together across models, the category of other disorders in children who died between 1 month and 59 months of age was generated to include congenital abnormalities, causes that originated during the perinatal period (eg, complications of preterm birth and intrapartum-related complications), cancer (registered in WHO mortality database),³⁰ pertussis, severe malnutrition, and other specified causes (see figure 1 for a summary of methods used for each country and the appendix (pp 43–46) for details of the estimation methods with comparison to those used previously⁸). To describe the trend, we applied the annual rate of change in cause-specific mortality rates using the following formula:³¹

$$r = \frac{\ln\left(\frac{CSMR_{T_2}}{CSMR_{T_1}}\right)}{T_2 - T_1} \times 100$$

where *r* is the annual rate of change, ln denotes the natural log function, CSMR is cause-specific mortality rate, and T1 and T2 each denote timepoints T1 and T2. Preliminary estimates were distributed to countries during the WHO country consultation process in December, 2011, and finalised after suggestions and any new data were incorporated when appropriate.

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. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Of 7.6 million children who died in the first 5 years of their life in 2010,¹ 64.0% (4.879 million) died of infectious causes (table 1). Of all infectious disorders, pneumonia, diarrhoea, and malaria were the leading causes of death worldwide (figure 2)—of all deaths in children younger than 5 years, pneumonia caused 1.396 million deaths (uncertainty range [UR] 1.189–1.642 million; 18.3% of total deaths), diarrhoea caused 0.801 million deaths (UR 0.555–1.182 million, 10.5%), and malaria caused 0.564 million deaths (UR 0.432–0.709 million, 7.4%). About 40% (3.072 million) of deaths in children younger than 5 years occurred in the neonatal period, most often because of preterm birth complications (14.1%; 1.078 million, UR 0.916–1.325 million), intrapartum-related complications (9.4%; 0.717 million, UR 0.610–0.876 million), and neonatal sepsis or meningitis (5.2%; 0.393 million, UR 0.252–0.552 million). Injury and congenital abnormalities were also important causes, with injury causing 0.354 million deaths (UR 0.274–0.429 million; 4.6%) and congenital abnormalities

	Estimated number (UR; millions)
Neonates aged 0–27 days	
Preterm birth complications	1.078 (0.916–1.325)
Intrapartum-related complications	0.717 (0.610–0.876)
Sepsis or meningitis	0.393 (0.252–0.552)
Pneumonia*	0.325 (0.209–0.470)
Congenital abnormalities	0.270 (0.207–0.366)
Other disorders	0.181 (0.115–0.284)
Tetanus	0.058 (0.020–0.276)
Diarrhoea†	0.050 (0.017–0.151)
Children aged 1–59 months	
Other neonatal disorders	1.356 (1.112–1.581)
Pneumonia*	1.071 (0.977–1.176)
Diarrhoea†	0.751 (0.538–1.031)
Malaria	0.564 (0.432–0.709)
Injury	0.354 (0.274–0.429)
Meningitis	0.180 (0.136–0.237)
AIDS	0.159 (0.131–0.185)
Measles	0.114 (0.092–0.176)

Uncertainty range (UR) is defined as the 2.5–97.5 percentile. Other disorders in children aged 1–59 months included congenital abnormalities, causes originated during the perinatal period, cancer, pertussis, severe malnutrition, and other specified causes. Intrapartum-related complications were formerly referred to as birth asphyxia. *The estimated number of deaths in children younger than 5 years overall is 1.396 million (UR 1.189 million–1.642 million). †The estimated number of deaths in children younger than 5 years overall is 0.801 million (UR 0.555 million–1.182 million).

Table 1: Estimated numbers of deaths by cause in 2010

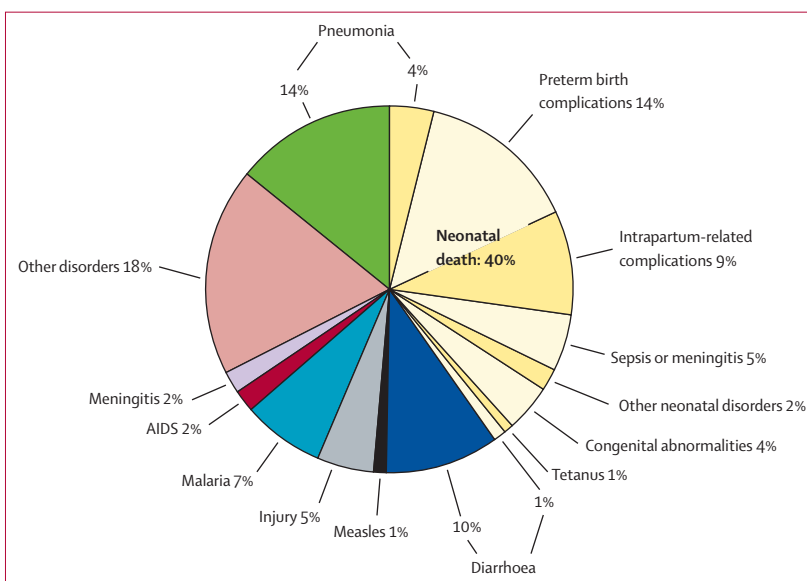


Figure 2: Global causes of childhood deaths in 2010
Causes that led to less than 1% of deaths are not shown.

causing 0.270 million deaths (UR 0.207–0.366 million; 3.5%) in children younger than 5 years.

The burden of mortality in children younger than 5 years varied widely across WHO regions in 2010, with the largest

number of deaths seen in Africa (3.6 million) and southeast Asia (2.1 million). However, different patterns of causes of child deaths were seen in the two regions (figure 3 and appendix pp 47–52). A striking 73.2% (2.600 million) of deaths in children younger than 5 years were due to infectious causes in Africa, which included 95.7% (0.540 million, UR 0.406–0.679 million) of global child deaths due to malaria and 89.5% (0.142 million, UR 0.115–0.166 million) of global child deaths due to AIDS. In 2010, neonatal mortality was highest in southeast Asia (1.096 million deaths, 52.3% of regional deaths in children younger than 5 years), with 19.2% of deaths (0.402 million,

UR 0.262–0.558 million) attributable to preterm birth complications, and 21.8% of deaths (0.457 million, UR 0.359–0.551 million) attributable to pneumonia in the neonatal and postneonatal periods.

India, Nigeria, Democratic Republic of the Congo, Pakistan, and China collectively accounted for half (49.3%, 3.754 million) the total number of global deaths in children younger than 5 years in 2010 (see appendix pp 53–57 for 2010 estimates for all 193 countries). These countries also accounted for half (2.440 million) the global deaths from infections and 53.3% (1.636 million) of neonatal deaths. In India, 1.682 million children

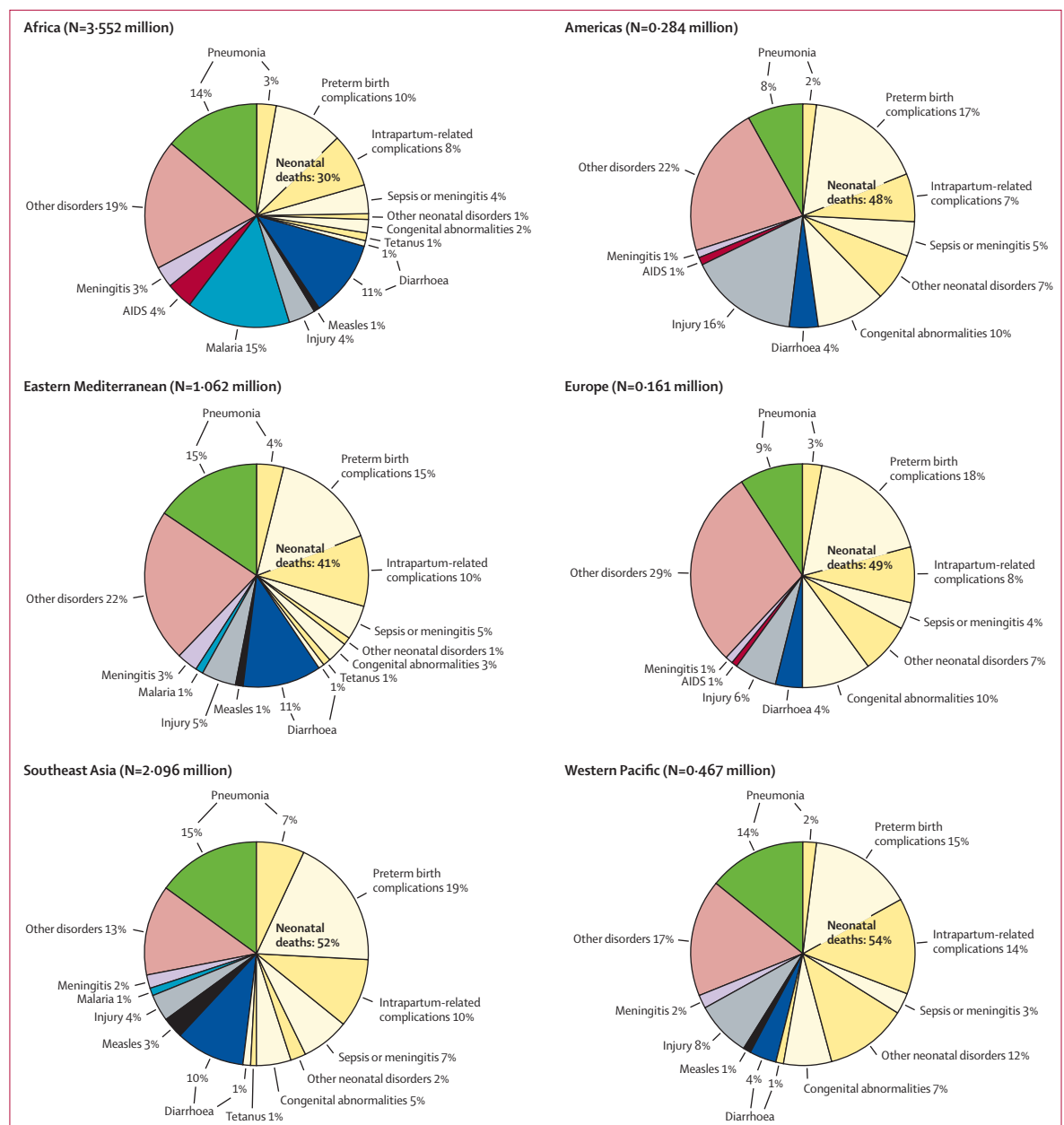


Figure 3: Regional causes of childhood deaths in 2010

younger than 5 years died in 2010 and more than half of them (52.0%, 0.875 million) died in the first 28 days of their life. Major causes of deaths included pneumonia (0.397 million, UR 0.302–0.484 million; 23.6%), preterm birth complications (0.304 million, UR 0.175–0.438 million; 18.1%), and diarrhoea (0.212 million, UR 0.181–0.275 million; 12.6%). In China, 0.315 million children younger than 5 years died in 2010 and 57.5% (0.181 million) of these deaths occurred in the neonatal period. The leading causes of death were pneumonia (0.055 million, UR 0.045–0.065 million; 17.4%), intrapartum-related complications (0.050 million, UR 0.044–0.056 million; 15.8%), and preterm birth complications (0.044 million, UR 0.037–0.049 million; 13.9%). For pneumonia and diarrhoea, the five countries with the most deaths were India, Nigeria, Democratic Republic of the Congo, Pakistan, and Ethiopia. The list of countries is similar for preterm birth complications and intrapartum-related complications, except that Ethiopia is replaced by China. Nigeria, Democratic Republic of the Congo, Burkina Faso, Mozambique, and Cote d'Ivoire had the most malaria deaths.

In 2000–10, despite global increases in the number of livebirths from 131.140 million to 134.683 million, and in the number of children younger than 5 years from 615.391 million to 633.555 million, the total number of deaths in children younger than 5 years decreased from 9.629 million to 7.622 million. Of the 2 million fewer deaths, four-fifths were attributable to the collective reduction in infectious causes. Specifically, during the past decade, deaths from pneumonia decreased by 0.451 million (UR 0.339–0.547), deaths from measles decreased by 0.363 million (UR 0.283–0.419), and deaths from diarrhoea decreased by 0.359 million (UR 0.215–0.476), contributing 22.5%, 18.1%, and 17.9% to the total reduction in deaths in children younger than 5 years in the past decade (figure 4).

During the same period, the U5MR reduced at an average rate of 2.6% per year,¹ which is less than 4.4% of the annual rate of decrease needed to reach MDG 4.³² All causes of death decreased in this period, albeit at differing rates (table 2 and appendix pp 58–64). Pneumonia deaths in all children younger than 5 years decreased from 1.847 million (UR 1.604–2.124) to 1.396 million (UR 1.189–1.642), with the pneumonia-specific mortality rate dropping by an average of 3.1% per year (UR 2.4–3.9%). Diarrhoea deaths in all children younger than 5 years decreased from 1.160 (UR 0.911–1.570) to 0.801 (UR 0.555–1.182) million, a 4.0% decrease (UR 2.4–5.6%) in the mortality rate per year during this period.

Overall, decreases in U5MR were faster in children aged 1–59 months than they were in neonates (2.9% per year vs 2.1% per year), so that the neonatal fraction of deaths increased from 38.2% (3.681 million) to 40.3% (3.072 million) in 2000–10. In neonates, the burden of preterm birth complications decreased from

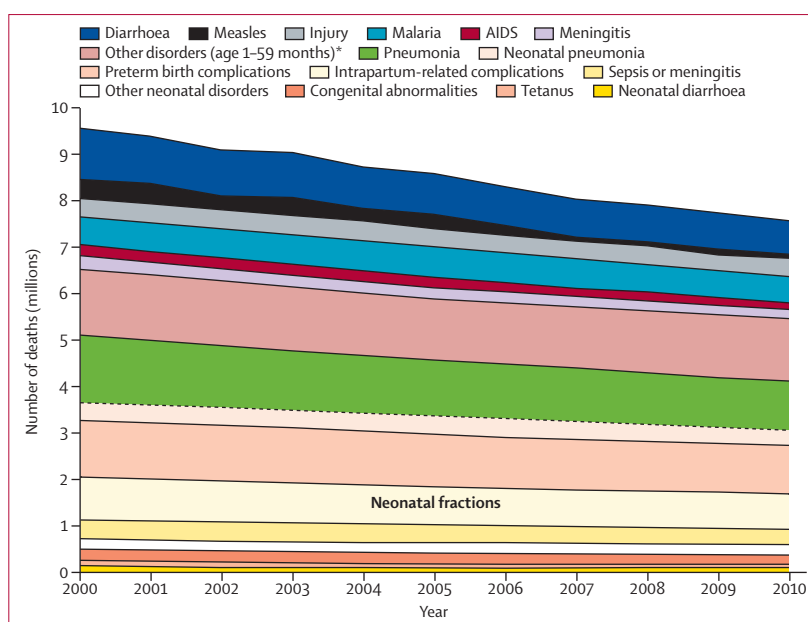


Figure 4: Global trends in burden of childhood deaths in 2000–10

*Includes congenital abnormalities, causes originated during the perinatal period, cancer, pertussis, severe malnutrition, and other specified causes.

1.281 million (UR 1.121–1.568) in 2000 to 1.078 million (UR 0.916–1.325) in 2010 at 2.0% (UR 1.6–2.6%) per year (table 2 and appendix pp 49–50). Intrapartum-related deaths decreased from 0.884 (UR 0.759–1.057) to 0.717 (UR 0.610–0.876) million at an average annual rate of 2.4% (UR 1.7–2.6%). Neonatal sepsis or meningitis also decreased, from 0.412 million (UR 0.323–0.541) in 2000 to 0.393 million (UR 0.252–0.552) in 2010, at 0.7% (UR –5.1% to 4.5%) per year, whereas neonatal tetanus decreased from 0.146 million (UR 0.068–0.590) to 0.058 million (UR 0.020–0.276) at 9.5% (UR 0.9–17.8%) per year. For children who died between the ages of 1 month and 59 months, trends in numbers and rates of deaths by cause were highly variable in 2000–10 (table 2 and appendix pp 51–52). The burden of malaria increased from 0.632 (UR 0.491–0.792) million in 2000 to 0.700 million (UR 0.540–0.875) in 2004, and then reduced to 0.564 million (UR 0.432–0.709) in 2010 at a rate of 4.0% (UR 3.1–4.7%) per year between 2004 and 2010 (data not shown). Measles mortality fluctuated greatly in this period, in part because of outbreaks of the disease, but overall it decreased from 0.477 million (UR 0.400–0.586) to 0.114 million (UR 0.092–0.176) at a rate of 14.6% (12.2–15.6%) per year.

Regional numbers and rates of child mortality by cause in 2000 and 2010 and the average annual rates of change in cause-specific mortality rates between 2000 and 2010 are shown in table 2 and the appendix (pp 47–52). During this period, U5MR decreased at varying rates across regions, with Africa and southeast

	World	Africa	Americas	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific
0-27 days*	-2.1	-1.5	-3.9	-1.4	-4.1	-2.3	-4.4
Pneumonia	-2.2 (-3.9 to -1.6)	-2.8 (-4.5 to -1.0)	-6.3 (-7.3 to -4.9)	-3.3 (-5.2 to -1.2)	-5.9 (-9.5 to -4.1)	-1.1 (-4.3 to 0.8)	-7.8 (-13.0 to -3.2)
Preterm birth complications	-2.0 (-2.6 to -1.6)	-1.4 (-2.5 to -0.2)	-5.1 (-5.4 to -5.0)	-1.2 (-2.2 to -0.1)	-4.3 (-4.8 to -3.4)	-2.1 (-3.1 to -1.1)	-4.7 (-5.4 to -3.8)
Intrapartum-related complications	-2.4 (-2.6 to -1.7)	-1.1 (-1.6 to -0.2)	-4.6 (-4.7 to -4.0)	-1.3 (-2.1 to -0.2)	-4.6 (-6.8 to -3.9)	-2.9 (-3.0 to -1.1)	-7.0 (-8.1 to -6.0)
Sepsis or meningitis	-0.7 (-5.1 to 4.5)	1.7 (-3.0 to 21.2)	-3.6 (-7.1 to 0.8)	7.1 (-1.6 to 40.0)	-5.5 (-6.6 to -3.1)	-3.9 (-10.7 to -0.1)	-3.8 (-8.8 to 2.7)
Other disorders	-1.7 (-2.0 to -0.9)	-1.1 (-2.2 to 0.8)	-2.1 (-2.9 to -1.9)	0.1 (-2.8 to 2.7)	-2.7 (-3.6 to -1.7)	-2.4 (-3.0 to -0.8)	-1.0 (-1.1 to -0.9)
Congenital abnormalities	-0.7 (-1.7 to 0.3)	-1.3 (-5.4 to 1.8)	-1.3 (-1.9 to -1.2)	-0.7 (-2.1 to 0.4)	-2.4 (-3.3 to -1.6)	-0.3 (-1.6 to 1.6)	0.0 (-3.1 to 3.4)
Tetanus	-9.5 (-17.8 to -0.9)	-11.1 (-19.5 to -1.0)	-8.4 (-17.3 to 2.4)	-12.1 (-21.5 to -3.0)	-17.8 (-26.6 to -10.5)	-5.5 (-13.0 to 5.2)	-14.3 (-20.8 to -6.3)
Diarrhoea	-4.0 (-6.7 to 0.1)	-4.1 (-6.9 to -1.2)	-12.3 (-16.5 to -8.4)	-5.7 (-12.4 to 0.8)	-6.1 (-8.3 to -3.1)	-3.4 (-7.3 to 2.7)	-5.4 (-15.0 to 3.1)
1-59 months*	-2.9	-2.9	-3.9	-2.1	-4.9	-4.5	-7.1
Diarrhoea	-4.0 (-5.5 to -2.4)	-3.7 (-5.8 to -1.9)	-10.1 (-12.1 to -8.6)	-3.2 (-5.3 to -0.9)	-7.7 (-10.3 to -5.1)	-5.2 (-5.7 to -4.7)	-9.9 (-13.9 to -8.8)
Measles	-14.6 (-15.6 to -12.2)	-20.9 (-24.9 to -16.1)	NA†	-17.3 (-19.4 to -13.8)	-27.2 (-32.8 to -9.6)	-6.2 (-6.6 to -5.3)	-14.5 (-16.6 to -11.1)
Injury	0.0 (-0.5 to 0.7)	1.2 (0.6 to 2.3)	5.8 (5.2 to 6.3)	0.4 (-0.2 to 1.3)	-5.1 (-6.2 to -3.8)	-1.6 (-2.4 to -0.8)	-4.7 (-6.3 to -3.5)
Malaria	-1.4 (-2.2 to -0.6)	-2.7 (-3.3 to -0.5)	-6.3 (-7.8 to -6.1)	-1.8 (-3.2 to 0.2)	-68.4 (-70.5 to -63.0)	-2.0 (-3.6 to -1.9)	-3.4 (-5.5 to -3.3)
AIDS	-4.8 (-6.4 to -3.0)	-6.4 (-8.3 to -4.5)	-8.4 (-10.0 to -4.8)	10.1 (3.2 to 16.4)	9.6 (1.6 to 14.1)	-2.7 (-8.9 to 4.1)	-0.1 (-6.0 to 5.5)
Meningitis	-4.1 (-6.7 to -2.5)	-2.8 (-6.6 to -0.2)	-9.4 (-11.1 to -8.8)	-3.4 (-7.1 to -0.2)	-10.1 (-11.1 to -8.6)	-6.1 (-7.9 to -4.6)	-9.2 (-14.8 to -5.5)
Other neonatal disorders	-0.9 (-1.7 to -0.2)	1.0 (0.5 to 1.8)	-4.8 (-5.4 to -4.5)	-0.5 (-1.4 to 0.3)	-3.1 (-3.9 to -2.6)	-3.7 (-4.1 to -3.0)	-4.6 (-13.0 to 2.5)
Pneumonia	-3.3 (-3.7 to -2.9)	-1.8 (-2.3 to -1.2)	-7.2 (-8.4 to -6.7)	-2.2 (-2.7 to -1.2)	-7.9 (-8.7 to -6.8)	-4.7 (-5.2 to -4.3)	-9.2 (-10.6 to -9.0)
0-59 months*	-2.6	-2.5	-3.9	-1.8	-4.5	-3.4	-5.7
Pneumonia	-3.1 (-3.9 to -2.4)	-2.0 (-2.6 to -1.3)	-7.0 (-8.2 to -6.3)	-2.4 (-3.1 to -1.4)	-7.5 (-8.4 to -6.4)	-3.6 (-5.2 to -2.6)	-9.0 (-10.3 to -7.6)
Diarrhoea	-4.0 (-5.6 to -2.4)	-3.7 (-5.6 to -2.0)	-10.2 (-12.0 to -8.5)	-3.3 (-5.5 to -1.1)	-7.7 (-10.1 to -5.1)	-5.1 (-5.9 to -4.2)	-9.2 (-12.5 to -6.2)

Data are annual rate of change (% [uncertainty range]). *The uncertainty ranges for children aged 0-27 days, 1-59 months, and 0-59 months were not available from the UN Interagency Group for Child Mortality Estimation at the time when this table was prepared. †There were no measles deaths in the region in 2010 and the annual rate of change, therefore, cannot be calculated.

Table 2: Global and regional average annual rate of change in cause-specific child mortality rates between 2000 and 2010, by age range and WHO region

Asia having the second and third slowest reductions (the slowest reduction was seen in the Eastern Mediterranean region; table 2), with average annual reductions of 2.5% and 3.4%, respectively. In Africa, the pneumonia-specific mortality rate decreased at an annual rate of 2.0% (UR 1.3-2.6%) in 2000-10. The malaria-specific mortality rate peaked in 2003 in Africa then decreased at a 4.5% (UR 3.2-5.0%) annual rate until 2010. In southeast Asia, mortality rates of pneumonia and preterm births decreased on average by 3.6% (UR 2.6-5.2%) and 2.1% (UR 1.1-3.1%) annually in this period. In the Americas, injury-specific mortality rate had been decreasing since 2000 but more than doubled from 2009 to 2010 because of the earthquake in Haiti. Additional details of the regional trends in the cause-specific mortality rates are shown in the appendix (pp 58-64). At the country level, varying trends in cause-specific death rates were seen in 2000-10. Numbers of child deaths by cause for all 193 countries in 2000 and cause-specific mortality rates for all 193 countries in 2000 and 2010 are shown in the appendix (pp 65-79).

Discussion

In 2010, of 7.6 million children who died before their fifth birthday, almost two-thirds died of infectious causes, nearly all of which were preventable. Two-fifths

of deaths in children younger than 5 years occurred in the first 28 days of their life, indicating the crucial importance of the reduction of neonatal deaths if countries are to achieve MDG 4.^{11,33} Preterm birth is now the second leading cause of child death after pneumonia, and is likely to become the top cause of death by 2015 unless rapid scale-up of available interventions occurs. The other leading killers of neonates were intrapartum-related complications and neonatal sepsis or meningitis. In older children, pneumonia, diarrhoea, and malaria were the most common causes of death.

In 2000-10, despite continued increases in the number of livebirths and the population of children younger than 5 years, the number of deaths in children younger than 5 years decreased by 26% (2 million deaths). Infectious causes decreased more rapidly than did non-communicable causes, with reductions in deaths caused by pneumonia, diarrhoea, and measles contributing most to the overall reduction. Major neonatal causes decreased at an annual rate that was at least one percentage point lower than that of major post-neonatal causes. Only a few causes, including tetanus, measles, and AIDS, reduced at a rate that was sufficient to achieve MDG 4, and these causes contribute only a small fraction of the overall burden of deaths in children younger than 5 years. However, the estimates of tetanus deaths in 2000 are much lower than the previous

estimates, and this discrepancy needs further investigation.^{34,35} The annual rate of reduction for tetanus could, therefore, be even higher than the estimated 9.5%. Of the remaining causes, the slow progress is especially concerning because accelerated reduction was estimated to have occurred in 2000–10 compared with 1990–2000,^{32,36} suggesting that merely maintaining the rate of change at the 2000–10 level will not be sufficient.

Five countries—India, Nigeria, Democratic Republic of the Congo, Pakistan, and China—contributed to almost half the world's deaths in children younger than 5 years. They also had half the mortality attributable to infections and more than half due to neonatal causes worldwide. Accelerated efforts to improve the survival of newborn babies and children in these countries are essential for achieving MDG 4. More aggressive efforts are also needed to scale up effective life-saving interventions in countries where insufficient or no progress had been made in the improvement of child survival since 1990.⁴

Our finding of a reduction in child deaths due to malaria is consistent with an estimate by Murray and colleagues³⁷ in which the global number of malaria deaths in children younger than 5 years peaked in 2004 but fell steeply afterwards.³⁷ However, our estimates are lower, for example by 29% in Africa in 2010,³⁷ although the uncertainty ranges overlap (0.540 million [UR 0.406–0.679] vs 0.699 million [UR 0.415–1.112]). The previous study³⁷ used verbal autopsy results from single-cause studies, which probably overestimate the fraction caused by malaria because they might erroneously classify a death as a malaria death on the basis that a child died with fever.³⁸ By applying the multi-site validation study to adjust for misclassification in the verbal autopsy studies, Murray and colleagues further inflated the study-level malaria fractions, which led to more estimated malaria deaths. However, the external validity of the multi-site validation study, which was done in areas with low prevalences of malaria, has not been shown.³⁹ Also, their malaria-specific fractions were derived with estimates of the number of deaths in children younger than 5 years that are lower than those used here,³ which further explains the differences in the fractions between the two studies.⁴⁰ Furthermore, the malaria estimates by Murray and colleagues were derived from a single-cause model and might have to be reduced when other important causes of death are estimated, and all must fit within the total number of deaths in children younger than 5 years.

Deaths from other disorders in children aged 1–59 months caused 17.8% (1.356 million, UR 1.112–1.581 million) of the global deaths in children younger than 5 years in 2010. These disorders include non-communicable causes (eg, cancer) and infectious causes (eg, pertussis). They also include severe malnutrition and other perinatal disorders such as prematurity and intrapartum-related complications. We combined these disorders into one category because the

fractions of some of these causes were either too small or available data were not sufficient to derive individual estimates. Improved estimates of specific disease burden within this category are needed.

CHERG has been progressively moving toward more application of the multi-cause models (panel),^{8,9} which we consider to be a scientific approach that is ideally suited for cause estimates that must sum to 100%. However, not all causes can be feasibly estimated in the multi-cause models. For causes contributing small fractions to mortality in children younger than 5 years, verbal autopsy studies do not capture sufficient deaths and the multi-cause model does not usually produce stable estimates. We therefore made the decision to apply single-cause models for uncommon disorders, including tetanus, measles, AIDS, and malaria in low-transmission countries on the basis of technical considerations. Compared with our previous estimation, additional changes made in this round to further advance study data and methods are included in the appendix (p 80).

Despite these advances, the updated child cause-of-death distribution in 2008 was still largely similar to our previous

Panel: Research in context

Systematic review

We systematically estimated the distribution of child mortality by cause at the national, regional, and global level for year 2010 with trends since 2000. Similar studies have been done by the same CHERG group over the past decade, during which time the input data and estimation methods have improved.^{8–12} To our knowledge, no other similar systematic estimation of the distribution of causes of child mortality has been published.

Interpretation

For high-mortality countries without adequate death registration, the estimation methods improved toward progressively more application of the multi-cause model. We consider this improvement as an important methodological advance that ensures that all causes fit the total number of deaths objectively. Furthermore, the time trends presented in our study provide information to better monitor the progress toward Millennium Development Goal (MDG) 4 and give the opportunity to better understand why some causes of death decreased at high rates while others decreased more slowly. The fact that our estimates are in close agreement with previous ones for 2008, despite data and method changes, adds to the reliability of our estimates. Across all the previous and current rounds of causes of childhood death estimation, pneumonia and preterm birth complications consistently rank as the leading causes at the global level. Africa and southeast Asia are repeatedly the regions with the most deaths in children younger than 5 years. Our trend analysis shows that accelerated reductions are needed in the two major causes and in the two high-burden regions to achieve the MDG 4 by 2015.

estimates in 2008,¹ with a few exceptions (appendix p 90). The most noticeable difference is that 14% of deaths in children younger than 5 years were estimated to be attributable to diarrhoea in 2008, compared with 11% in this study. Further analysis showed that the difference was mainly driven by the newly included verbal autopsy studies, which were done more recently and reported fewer diarrhoea deaths (appendix p82). 0·867 million fewer deaths in children younger than 5 years were estimated to have occurred in 2008 since our last estimate. As a result, the numbers of deaths due to most causes was noticeably smaller than our previous estimates, despite similar cause-specific fractions. Direct comparison between results published here with CHERG's previous estimates would be ill-advised. The differences do not show the actual trends, which are shown in this paper.

Notwithstanding intensive efforts to identify childhood cause-of-death studies, scarcity of data is still the major obstacle for improved estimation. Medically certified vital registration data were available for only 61 countries or 2·7% (0·205 million) of 7·6 million deaths in children younger than 5 years in 2010 (figure 1). Where mortality rates and the need for data are the highest, resources and data are the least available, with the evidence gap especially acute in sub-Saharan Africa. This gap has been recognised by the global child survival community, and more empirical data for causes of childhood deaths are being collected and shared in low-income and middle-income countries.³⁹ CHERG is actively seeking to include more national empirical data in future analyses and plans to publish more subnational analyses for large countries. Few verbal autopsy studies are available in settings where rapid scale-up of child-survival interventions were rolled out during the past decade. Because of the scarcity of data, we had to resort to post-hoc adjustments to account for the effect of these interventions. With more recent studies providing information about these interventions, such post-hoc adjustment could hopefully be eliminated from the estimation process.

Among the verbal autopsy studies included in the modelling process, measurement issues were problematic. Verbal autopsy studies are subject to known inherent misclassification errors,⁴¹ which can lead to inaccurate estimation of the cause-of-death distribution. We made many attempts to obtain study covariates via author requests but only a few authors replied to provide additional information. In many cases, the required information was not readily available from the studies, and data were obtained from alternative sources. Consequently, the actual variability of the study covariates was not fully represented, which could result in a model with a biased relation between causes of deaths and explanatory variables. These issues, however, can be alleviated only when the distribution of child causes of deaths and coverage of key childhood interventions are better measured and reported.⁴

Global, regional, and national childhood cause-of-death estimates should enable the setting of priorities for scaling up child survival interventions and guide national and international resource allocation. The attainment of MDG 4 is possible only if life-saving maternal, newborn, and child health interventions are rapidly scaled up in high-burden regions and countries and across major causes in the next few years. CHERG endeavours to provide scientific evidence to support this process and strives to make the estimation as transparent and replicable as possible. Continued efforts to gather high-quality data and enhance estimation methods are essential to improve future estimates. We challenge countries and the entire global health community to promote registration and medical certification of deaths and strengthen national health information systems to enable better accountability for the survival of children.⁴²

Contributors

LL analysed of the postneonatal VAMCM and wrote the first draft of the paper. HLJ collected study data for the VAMCM and analysed the postneonatal VRMCM. SC, SS, and JEL did all analyses for neonates. SC and JEL edited the paper. JP ran all cross-validation and uncertainty estimation. IR and HC did the analysis for China. RC derived malaria estimates for low-transmission countries and provided feedback for high-transmission countries. ML prepared the prediction database, study covariates, tables, figures, and appendices of the paper under the supervision of LL. CM provided the total number of deaths by age, did the analysis of vital registration data, combined results across models, and did all country consultation. REB supervised all analyses and edited the paper. All investigators provided feedback to the estimates at various points during the analyses and contributed to the subsequent versions of the paper. CHERG members critiqued preliminary methods and results of this updated analysis.

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Conflicts of interest

We declare that we have no conflicts of interest.

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