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transformed study-level incidence on the log-transformed malaria mortality rate, age-group indicators, a sub-Saharan Africa indicator, an indicator distinguishing active versus passive case detection (set to active when generating predictions), and the ratio of the site-specific PfPR to national PfPR (from MAP 2010; set to the value 1 when generating predictions so that the estimates are nationally representative). In this model, the incidence data came from available studies and the mortality data came from our CODEm analysis. The second group included countries for which there were incomplete administrative data, for which we predicted malaria incidence by regressing incidence data from the World Malaria Report 2013 on national-level PfPR. We corrected for underreporting using a composite indicator for health system access as a proxy. The third group contained countries with complete and reliable administrative case reports, for which we used reported numbers as published in the World Malaria Report.

CoDCorrect algorithm

As with all causes of death analysed for the GBD, we require that the sum of each individual cause of death for a country, age, sex, and year equals the estimate of all-cause mortality. The CoDCorrect algorithm rescales the sum of causes at the individual draw level. The effect of this simple algorithm is to change causes that have larger uncertainty intervals if there is a mismatch between the sum of cause-specific mortality and all-cause mortality. To preserve the relations between incidence, prevalence, and death that come from the Spectrum analysis, the entire epidemic curve for HIV is scaled in CoDCorrect.

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 for publication.

Results

Figure 7 shows the estimated trend in global numbers of incident cases, people living with HIV (prevalence), and deaths from HIV. Global HIV incidence peaked in 1997 with 2·8 million (95% uncertainty intervals 2·7 to 3·1) new infections and has since decreased at 2·7% (2·0 to 3·1) per year. From 1997 to 2005, incidence decreased at 3·8% (3·0 to 4·6) per year and from 2005 to 2013 at 1·6% (0·6 to 2·4) per year. New infections in children decreased from 340 000 (323 000 to 363 000) in 2000 to 134 000 (123 000 to 152 000) in 2013 at an annualised rate of change (ARC) of −7·2% (−7·8 to −6·4%), while new infections in adults decreased from 2·3 million (2·1 million to 2·4 million) to 1·7 million (1·6 million to 2·0 million), falling at 2·4% (1·6 to 3·0) per year, on average, during this period. Annual incidence estimated by UNAIDS is uniformly higher in the years shown and shows a sharper rate of decrease. Prevalence of individuals infected with HIV has steadily risen to 29·2 million (28·1 million to 31·7 million) in 2013 rising more rapidly from 1990 until about 2000 at an annual rate of change of 10·6% (10·1 to 11·3), and increasing at 1·2% (0·9 to 1·4) per year since (figure 7). Compared with UNAIDS's estimations, our estimation for 2012 suggest 6·6 million fewer individuals living with HIV. 32·0% of this difference is in sub-Saharan Africa and 68·0% is elsewhere. Figure 7 shows trends for HIV deaths compared

with UNAIDS estimations, with a peak mortality of 1·7 million (1·6 million to 1·9 million) in 2005. Annual mortality has subsequently fallen to 1·3 million (1·3 million to 1·5 million) in 2013, an ARC of −3·1% (−4·0 to 2·2). While the time trend of mortality estimated by UNAIDS is similar to ours, the estimated number of deaths is substantially greater. At the peak of the epidemic in 2005, our revised assessment of the HIV epidemic suggests 635 000 fewer deaths than UNAIDS's estimates, although the difference (240 000) narrows substantially by 2012, the last year available from UNAIDS. For the interval 2005–12, the UNAIDS ARC for death numbers was −5·0% (−5·6 to −4·5), reflecting the lower assumed death rates on ART in the UNAIDS version of Spectrum.

New HIV infections are concentrated in young adults and to a much lesser extent, in children under 5 years of age (figure 8); 4·1% (3·8 to 4·5) of new infections occur in idividuals older than 60 years. New cases in 2013 occurred equally in both sexes. However, there are more infections in women than men at ages 15–24 years. Incidence in children, and in older adults, is similar for both sexes. Showing a mean survival time of more than 10 years in most countries and age-groups, the age pattern of deaths peaks in women at ages 35–39 years and in men at 40–44 years (figure 8). More deaths are in male individuals (53·9% [51·9 to 56·1]) than in female individuals. The proportion of deaths that occur beyond age 60 years (6·8% [6·2 to 7·4]) is larger than the proportion of incident cases that occur beyond age 60 years (4·1% [3·8 to 4·5]).

Table 2 shows the ARCs for 1990–2000 and 2000–13 for incidence, prevalence, and death for the 21 GBD regions and the world. ARCs between two fixed time periods need to be interpreted bearing in mind that measures of the HIV epidemic such as incidence and death will have peaked and decreased in particular countries at different times during the interval. Nevertheless, our findings show the accelerated progress in most of the world's regions. The only regions with a reversal in the ARC such that incidence was decreasing but in the later period is increasing or stagnating are southeast Asia, high-income North America, western Europe, Australasia, and Tropical Latin America. The reversal in southeast Asia can be explained by the large decrease in the 1990s achieved by a successful campaign to reduce infection through commercial sex encounters in Thailand, the country in the region with the largest epidemic. The reversal of incidence trends in North America might show a wearing off of the effect of public health measures to reduce the risk of transmission in men who have sex with men.

Age-standardised HIV incidence rates per 100 000 population (figure 9) in 2013 ranged from less than 0·7 in a group of countries ringing the Eastern Mediterranean, parts of northern and central Europe, and Mongolia, to more than 570 in South Africa, Lesotho, and Swaziland. HIV infection follows distinct geographic patterns with continued high levels of infection throughout eastern and southern Africa, with some exceptions. Rwanda, Burundi, DR Congo, Congo, and Gabon all have incidence rates less than 120 per 100 000 population, lower than their neighbouring countries. Incidence rates vary widely in sub-Saharan Africa, but are more homogenous across countries in Asia as well as North and South America. Important exceptions to these patterns include incidence rates above 15 per 100 000 population in many Caribbean countries. Incidence rates are notably higher in Portugal and Ukraine, as well as Russia and some Central Asian republics. Figure 9 shows

prevalence rates in countries in 2013. Geographical patterns are similar to incidence, although some differences are noteworthy. Prevalence levels are highest in Botswana, Lesotho, and Swaziland (above 12 000 per 100 000 population). There is substantial variation within sub-Saharan Africa; prevalence rates in Botswana, for example, are 15 times higher than in the DR Congo and 40 times higher than in Niger. In southeast Asia, prevalence is substantially higher in Thailand and Papua New Guinea. Prevalence rates are comparatively high in parts of Europe and central Asia (Portugal, Spain, Ukraine, Russia, and Kazakhstan) and in Latin America and the Caribbean (Panama, Honduras, Belize, Guatemala, Guyana, Suriname, Haiti, Dominican Republic, Jamaica, and Bahamas) prevalence levels exceed 220 per 100 000 population. Comparison of incidence and prevalence in figure 9 draws attention to some differences for countries in their comparative ranking, such as for Sweden and Australia. Cross-national variations in HIV mortality rates per 100 000 population, largely mirror the pattern reported for prevalence, varying from less than 0·2 in northern and central Europe and the Eastern Mediterranean, to more than 520 in southern Africa, a roughly 2500-fold difference (figure 10). Table 3 shows more detail on the estimated number of new infections and deaths in 2013 for both sexes, individually and combined, for 188 countries, along with ARCs in age-standardised incidence and death rates for both sexes combined.

By comparing the estimated number of person-years lived in a no-intervention scenario with actual estimates, we can compute the years of life saved through ART, PMTCT, and co-trimoxazole prophylaxis. Figure 11 shows cumulative years of life saved by GBD region as a result of these interventions during three phases of scale-up. From 1990 to 2003, 1·5 million years of life (1·2 million to 1·9 million) were saved, of which only 22·7% (14·2 to 32·1) were in populations living in developing countries, largely in Brazil. The number of years of life saved increased substantially in the period 2004 to 2008 to 3·9 million (3·2 million to 4·7 million), and the share in populations in developing countries increased to 52·6% (44·1 to 62·2). Between 2009 and 2013, the number of life-years saved was 13·7 million (11·8 million to 15·7 million). A much greater share (40·8% [33·8 to 47·6]) of these life-years saved were in eastern and southern sub-Saharan Africa, and a further 12·1% (9·0 to 15·7) in western sub-Saharan Africa. Other regions to benefit substantially from HIV interventions include high-income North America, western Europe, and south Asia. The number of years of life saved continues to grow rapidly due both to the continued expansion of ART and the cumulative effect of infections prevented in children. By 2013, the global cumulative number of years of life saved was 19·1 million (16·6 million to 21·5 million); 14·2% (12·4 to 16·2) at ages younger than 15 years, 49·7% (45·8 to 53·4) at age 15–49 years, and 36·1% (32·7 to 39·5) at 50 years of age or older.

Since 2000, cumulative DAH for HIV up through 2011 totals $51·6 billion, of which $32·7 billion can be traced to specific developing country programmes in 2011 US dollars.[109] Comparison of the total amount invested in HIV prevention and treatment to the years of life saved during 2000–11 yields in developing countries a ratio of $4498 per life-year saved. The ratio of DAH for HIV to years of life saved varies widely from $2·38 in Uruguay per life-year saved to $1·87 million in Mongolia per life-year saved.

The scale-up of ART has been variable across countries. Because of the temporal dynamics of the epidemic in different countries, comparisons of intervention scale-up are confounded by the timing of incidence. Nevertheless, the appendix (p 22) shows a crude comparison of years of life saved over the age of 15 years divided by prevalent cases in people older than 15 years in 2013. This ratio ranges from less than 0·07 in countries with minimal intervention to more than 0·49 in many high-income countries. In developing countries, Brazil stands out with a ratio of 0·37. In the next tier, with ratios between 0·28 and 0·35 includes many countries in Latin America and Botswana, Namibia, Thailand, Cambodia, South Korea, and some countries in central Europe. In eastern and southern Africa, Ethiopia, Rwanda, and Burundi we saw higher ratios than in many of their neighbouring countries. Pronounced variation within regions points to the historical variation in the timing of the epidemic response.

Figure 12 shows a comparison of our estimated prevalence for country-age-sex groups against national population prevalence surveys. This comparison provides a rough check that at the end of the modelling process our assessment remains consistent with population-based prevalence measurements as well as being consistent with data for all-cause mortality. In general, there is a strong correlation (0·96) of our country-age-sex estimates with survey prevalence—UNAIDS prevalence is also correlated (0·96) with survey data. However, in 21% of cases, there is a statistically significant difference (19% for UNAIDS). The coefficients obtained by regressing both GBD and UNAIDS estimates on survey estimates showed that both methods tended to be slightly higher than the surveys; however, only the UNAIDS coefficient was a statistically significantly larger than one: UNAIDS, 1·08 (1·03 to 1·13); GBD, 1·02 (0·98 to 1·06). Country-specific graphs comparing GBD, UNAIDS, and survey prevalences by age and sex are shown in the appendix (p 24).

Figure 13 shows the temporal changes of tuberculosis incident case numbers, the number of prevalent cases, and the number of deaths from 1990 to 2013. Total tuberculosis numbers are shown as well as numbers for tuberculosis in individuals who are HIV-negative. The number of incident cases for tuberculosis in individuals who are HIV-negative has increased from 5·0 million (4·8 million to 5·1 million) in 1990 to 7·1 million (6·9 million to 7·3 million) in 2013—a 1·5% (1·4 to 1·6) annual change. Prevalence in 1990 and 2013 was 1·6 times higher than incidence, implying a duration of 20 months on average for a case. Prevalence rates increased slightly between 1990 and 2000 (ARC 0·4% [0·2 to 0·6]) but decreased by 1·3% (1·4 to 1·2) per year from 2000 to 2013. Deaths from tuberculosis in individuals who are HIV-negative are decreasing at a faster rate, from 1·8 million (1·7 million to 1·9 million) in 1990 to 1·3 million (1·2 million to 1·4 million) in 2013—a −1·4% (−1·9 to −1·0) annual change. Decreases in death numbers and increases in incidence numbers implies that the case-fatality rate has been falling over the period; the ratio of deaths to incidence overall went from 0·36 (0·33 to 0·39) in 1990 to 0·18 (0·16 to 0·20) in 2013—a −2·9% (−3·4 to −2·5) per year rate of change. Most global tuberculosis incidence cases and deaths in individuals who are HIV-negative are in men and boys, 64·0% (63·6 to 64·3) for incidence and 64·7% (60·8 to 70·3) for mortality (figure 14). Although age-specific rates rise with age up to 70 years, in view of the comparatively young age-structure of countries with substantial burden of tuberculosis in individuals who are HIV-negative,

83·2% (82·6 to 83·8) of cases and 58·8% (56·7 to 60·6) of deaths were in people younger than 60 years in 2013.

Table 4 shows a summary at the global and regional level of the ARCs for age-standardised rates of incidence, prevalence, and deaths for tuberculosis in individuals who are HIV-negative (see the appendix p 203 for tuberculosis including HIV-positive individuals). At the global level, age-standardised mortality rates decreased by 3·3% (4·1 to 2·6), whereas incidence remained stable (0·0% [−0·2 to 0·2]) and prevalence rates increased by 0·4% (0·2 to 0·6) during the period 1990 to 2000. Global decreases continued in the period 2000 to 2013 for mortality (−3·7% [−4·4 to −3·0]) whereas incidence decreased by 0·6% (0·7 to 0·5) and prevalence decreased by 1·3% (1·4 to 1·2). Across regions, in the period 2000 to 2013, incidence rate ARCs in individuals who are HIV-negative ranged from 0·8% (0·6 to 1·0) in Oceania to −3·3% (−3·6 to −3·1) in high-income North America. 16 of 21 regions had a greater decrease (or at least a smaller increase) in the incidence rate from 2000 to 2013 than for 1990 to 2000. Mortality rate decreases in HIV-negative individuals were greater in the period 2000 to 2013 than the decreases in prevalence in all 21 regions. The global decline in prevalence from 2000 to 2013 is largely accounted for by the large decreases in just two regions: east and south Asia. In south Asia, which accounts for 34·8% (33·9 to 35·6) of incident cases and 47·7% (43·5 to 51·8) of deaths in 2013, the ARCs for 2000 to 2013 were −1·1% (−1·3 to −0·8) for incidence, −2·4% (−2·7 to −2·2) for prevalence, and −4·2% (−5·6 to −2·9) for mortality. Accelerated decreases in prevalence, incidence and mortality occurred in east Asia from 2000 to 2013: −3·2% (−3·4 to −2·9) for prevalence, −2·1% (−2·4 to −1·9) for incidence, and −7·5% (−8·5 to −6·6) for mortality. The tuberculosis trend in eastern Europe has reversed: in the 1990s, mortality, incidence, and prevalence rates were all increasing, with ARCs of 8·3% (5·5 to 9·1), 1·3% (1·0 to 1·7), and 1·7% (1·4 to 2·0), respectively. However, in the period 2000 to 2013 the trends for all three of these indicators have improved, with ARCs of −4·8% (−7·6 to −3·9), −0·6% (−0·8 to −0·4), and −0·7% (−1·0 to −0·5). Table 5 shows incidence and deaths by country in 2013 along with ARCs for age-standardised rates.

Figure 15 shows maps of age-standardised incidence rates and death rates for tuberculosis in individuals who are HIV-negative in 2013. Age-standardised incidence of tuberculosis in individuals who are HIV-negative is more than 200 per 100 000 population in 24 countries in sub-Saharan Africa as well as in North Korea, Timor-Leste, Cambodia, Laos, Philippines, and Kiribati (figure 15). There are an additional 16 countries with rates of more than 150 per 100 000 population that include Bangladesh, Myanmar, India, Pakistan, Ethiopia, and Malawi. Figure 15 also shows tuberculosis death rates in individuals who are HIV-negative which are above 10 per 100 000 population in all countries in sub-Saharan Africa and increase to more than 50 per 100 000 population in 40 countries. Among middle-income countries outside of sub-Saharan Africa, Afghanistan, Indonesia, India, Myanmar, and the Philippines stand out as countries with death rates higher than 50 per 100 000 population. The highest age-standardised death rates in Latin America and the Caribbean are in Haiti followed by Bolivia and Peru. Death rates per 100 000 population are highly variable in north Africa and the Middle East, ranging from very low in Syria (0·5 [0·3 to 0·9]) and Jordan (0·8 [0·6 to 1·0]) to high in Morocco [14·3 [11·2 to 17·5]) and Yemen (19·9 [11·5 to 41·5]) in 2013. Eastern Europe and central Asia stand out with death rates that are

substantially higher than western or central Europe. China has lower rates of death than eastern Europe and central Asia. Our findings are mostly consistent with the list of high-burden countries used by WHO; however, our top 22 countries in terms of case numbers or death numbers that are not on the WHO high-burden list include South Korea, North Korea, and Madagascar for case numbers and Angola and Zambia for mortality. WHO high-burden countries that did not make our top 22 list for case numbers include Afghanistan, Cambodia, and Tanzania, and the WHO high-burden countries that did not make our top 22 list for mortality include Brazil and Cambodia.

Trends in the annual number of new cases of malaria, and annual deaths from malaria, are shown in figure 16 for the period since 1990. Global incidence seems to have peaked in 2003 at 232 million cases (143 million to 387 million) and has since fallen by about 29% to 165 million new cases (95 million to 284 million) in 2013. There is massive uncertainty around these estimates: the 2013 estimate, for example, could be anywhere between 95 million and 284 million. The estimates of new malaria cases in the World Malaria Report fall within the uncertainty intervals of the GBD estimates with a mean number of new cases in 2012 of 207 million (135 million to 287 million). By contrast with incidence data, the World Malaria Report estimates of malaria deaths are slightly lower (figure 16). There are also some important differences in the timing of the peak and decline in malaria mortality. Annual malaria deaths began to decline from a peak of 1·2 million (1·1 million to 1·4 million) in 2004 to about 855 000 (703 000 to 1 032 000) in 2013, having increased from 888 000 (793 000 to 993 000) in 1990. According to the World Malaria Report,[110] malaria caused about 627 000 deaths in 2012, having reached a peak of about 900 000 around the turn of the century. The age-sex pattern of global malaria incident cases and deaths in 2013 is shown in figure 17. The largest number of cases is in people younger than 15 years. Malaria deaths, by contrast, are concentrated in children younger than 5 years, although malaria caused between 10 000 and 25 000 deaths in each 5-year age group beyond age 15 years, so that the cumulative fraction of malaria deaths in adults reaches 33·75%.

Globally, age-standardised malaria incidence and death rates were increasing in the period 1990–2000 (table 6), but many regions outside of sub-Saharan Africa and north Africa and the Middle East had decreases in age-standardised incidence, death rates, or both. In the period since 2000, all regions including sub-Saharan Africa had decreases in age-standardised incidence and death rates. Incidence decreased by 38% (37 to 40) in central Asia since 2000, a result of increased malaria elimination efforts in the region. Figure 18 shows the geographical distribution of the age-standardised incidence rate in 2013. The geographical distribution of the age-standardised mortality rate (figure 18) shows a similar pattern with the highest rates in Mozambique, Burkina Faso, Guinea-Bissau, Mali, Sierra Leone, The Gambia, and Guinea. Rwanda stands out as having low rates compared with its neighbouring countries. Outside of Africa, Yemen, India, Myanmar, and Papua New Guinea have death rates higher than 7·5 per 100 000 population. In southeast Asia, Thailand and Malaysia have achieved very low death rates. Table 7 shows incidence and death numbers by country in 2013 along with ARCs for age-standardised rates. Four countries have over 5 million cases a year including India with over 60 million cases, Nigeria (30 million), DR Congo (with 6 million), and Mozambique (6 million). Three countries—Nigeria, DR Congo, and India—account for roughly 50% of all malaria deaths in 2013.

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Discussion

HIV, tuberculosis, and malaria remain major health challenges in 2013. The mean age of death differs substantially between them, at 15·3 years for malaria, 38·6 years for HIV, and 52·9 years for tuberculosis in HIV-negative individuals, which means that the burden in terms of years of life lost varies across the diseases. Tuberculosis deaths have decreased globally since 1990, and after 2000 incidence, prevalence, and death have all decreased. HIV incidence peaked in 1997 and mortality peaked in 2005 with substantial declines since the peak in each. Malaria incidence and mortality peaked and began declining in 2004 with substantial drops in the number of child deaths in sub-Saharan Africa over the past 5 years. There is substantial variation both in levels and trends for all three diseases across countries. HIV and malaria incidence and death are concentrated in sub-Saharan Africa whereas tuberculosis burden is more widespread but most pronounced in south and southeast Asia.

From our analysis of HIV data, our findings show that the HIV epidemic is smaller than estimated by UNAIDS. Our global epidemic curve for mortality ranges was lower than estimated by UNAIDS for every year; at the peak in 2005 our estimates are 27·0% lower and in 2012 are 14·5% lower. Our estimates of global prevalence differ from UNAIDS's by 17·1% in 2005 and 18·7% in 2012. The substantial differences in the number of deaths stem from two key differences in these analyses. First, in the 125 concentrated epidemics with some cause of death data for mortality due to HIV, our estimated mortality is 52·2% lower in 2000 and 58·4% lower in 2012 than UNAIDS's estimates. Our prevalence estimates are, for example, 36·3% lower for Panama, 52·2% lower for Colombia, and 58·4% lower in Russia. Second, in the large generalised epidemics, selecting epidemic curves that are consistent with prevalence data, all-cause mortality, and available studies on survival with and without ART shifted median survival up. For example, in southern Africa, median survival off ART for the age-group 25–34 years increased from 10·5 years to 11·5 years. Longer or shorter survival off ART in some countries could be explained by genetic factors,[111-115] co-factors such as the presence of other diseases like malaria,[116-118] differential access to treatments for opportunistic infections, or other co-factors that have not been described. These findings are important in terms of identifying the magnitude and comparative burden of HIV. Table 8 outlines the differences between our HIV/AIDS estimation strategy and that of UNAIDS.

Comparison of population-based surveys with our estimates of prevalence suggest reasonable alignment and the regression analysis of estimated prevalence on measured prevalence suggest there is not systematic tendency in our estimates to overestimate or under estimate prevalence. However, much variation exists by age and sex with nearly one in five of our age-sex specific prevalence estimates statistically different than the survey prevalences. Several potential explanations for this variation exist. Our assumptions about the relative incidence pattern by country might not be true at the local level. Differential non-response in the surveys by age and sex is also a potential factor. The adjustments made through the demographic matching and CoDCorrect algorithm could contribute to the differences. More analysis on a country-by-country basis will be helpful in exploring these issues in future research.

Revisions of the global epidemiology of HIV of this magnitude—in view of the weakness of direct measurement of incidence and death—should not be surprising. As prevalence surveys became more widely available, UNAIDS revised downward their global prevalence estimates by 18% in 2007 and their global mortality estimates by nearly 24%.[119] Taking into account more data for survival on and off ART and incorporating all-cause mortality data has led to revisions of a similar magnitude. Our revisions also suggests that there is greater uncertainty for incidence, prevalence, and death than previously estimated. Irrespective of the specific estimates generated from imperfect data, however, our assessment of prevalence continues to point to the very large and steadily growing numbers of infected individuals, many of whom are in need of antiretroviral therapy. Great progress has been achieved reducing infections in children (62·4% reduction since the incidence peak in 2002) due to the scale-up of interventions. The continued 1·7 million new infections per year in adults, down 32·7% from the peak of the epidemic at the global scale, however, is a stark reminder of the continuing epidemic.

A key finding that confirms many local, regional, and global studies[120-125] is that interventions, especially ART, PMTCT, and co-trimoxazole, have had a profound effect. Cumulatively, 19·1 million years of life have been saved since 1996, 5·7 million in developed countries and 13·4 million in developing countries, where the ratio of DAH to years of life saved is less than $4500 for the average of the period 2000–11. In view of the very rapid increase in years of life saved in 2012 and 2013, the ratio for the period 2000–13 when DAH figures are available will probably be much lower. The scale-up, number of lives saved, and comparatively low price per year of life saved is one of the major achievements in global health in the past decade. Many groups—local, national, and global—deserve credit for this accomplishment. DAH does not count national contributions to the cost of HIV programmes; real variation in the ratio of the total cost per year of life saved is probably much smaller because many middle-income countries receive little DAH and fund most HIV interventions from their own resources. Micro-economic studies of the cost per years of life saved have also reported wide variation across locations.[126-128] We would expect, given investments in initial programme start-up including capital equipment investments, that the ratio of DAH to life-years saved will decrease over time. With prevalence growing 5·8% per year over the past 5 years, the need to learn from more efficient programmes is paramount. Our analysis of survival on ART shows wide variation in programme outcomes within sub-Saharan Africa. Counterfactual analysis of what might happen if all programmes achieved the levels of mortality seen in the programmes with the best outcomes or even what would happen if high-income country on-ART death rates were achieved would help shed further light on the importance of quality improvement for future HIV death reductions. Improving cost-effectiveness of ART programmes will require a process of continuously documenting costs, outcomes, and efficiency along with a mechanism for shared learning across programmes on improving quality. HIV infected intravenous drug users have not benefited as much from treatment as those infected through sexual transmission. Regions with an ongoing increase in mortality from HIV in the 2000–13 period are high-income Asia Pacific, central and eastern Asia, eastern and central Europe, north Africa and the Middle East, Oceania, and southern and western sub-Saharan. In a number of these regions large proportions of HIV cases are in intravenous drug users for

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whom countries might be less inclined to provide treatment services. Even in countries with a greater emphasis on harm-reduction strategies, drug users might still be a more difficult group for health services to reach.[129]

Age-standardised tuberculosis mortality rates including tuberculosis in HIV-positive individuals at the global level changed at −2·8% (−3·6 to −2·2) per year from 1990 to 2000 and around a percentage point faster from 2000 to 2013 (−3·7% [−4·4 to −3·0%]) per year. When examining tuberculosis mortality in individuals who are HIV-negative, the acceleration was smaller, from −3·3 (−4·1 to −2·6) to −3·7% (−4·4 to −3·0) change per year but still statistically significant. There has been comparatively little decrease in the global age-standardised tuberculosis incidence rates in HIV-negative individuals although some regions such as south Asia and east Asia have seen accelerated declines since 2000. Prevalence has decreased much faster than incidence, which is consistent with earlier and more effective treatment-shortening durations. In addition to shorter duration, the death to incidence ratio changed from 0·36 in 1990 to 0·18 in 2013, also a likely consequence of treatment. There has been much regional and country variation in progress on tuberculosis with the ARC for mortality ranging from −10·3% to 2·5% from 1990 to 2013 and the ARC for incidence ranging from −3·3% to 2·5% over the same period. This variation implies that more rapid progress is possible at the global scale if lessons can be learned from countries with more rapid achievement. Since 2000, as for HIV and malaria, global progress in terms of prevalence and mortality has accelerated. We are unable to compute the extra years of life saved for tuberculosis as we can for HIV; but the comparatively small DAH for tuberculosis over the period 2000–11 ($8·3 billion) has been associated over this time period with greater reductions in incidence, prevalence, and death rates. Tuberculosis is different from HIV and malaria in that the rising incidence and death rates with age mean that demographic ageing of the world's population in the absence of other changes will naturally lead to higher numbers of cases and deaths. Demographic changes in essence slow the progress of tuberculosis control; a factor that should be built into considerations of funding and programme strategy. The established links between alcohol, diabetes, tobacco smoking and tuberculosis also mean that trends in these risk factors can modulate trends in tuberculosis.[131-133] In this analysis, we have not separately examined the incidence, prevalence, and mortality related to multi-drug resistant tuberculosis (MDR-TB). There are concerns that even in places with substantial decreases in tuberculosis incidence, prevalence, and death such as in China, MDR-TB might be a substantial challenge.[82,133-136] Modelling studies have shown that under specific circumstances MDR-TB could reverse important gains made in combatting tuberculosis.[82,136,137] Future revisions of the burden of disease should examine more carefully the evidence on the levels and trends in MDR-TB.

Our results for tuberculosis differ from WHO estimates in some important ways. In general, we estimate higher mortality, lower prevalence and incidence, and a smaller fraction of tuberculosis related to HIV. Our estimates of prevalence are driven by the available prevalence surveys and are not back calculated from incidence. Our incidence estimates start with case-notifications corrected for missing age-groups and case types such as smear-negative pulmonary or extrapulmonary and expert judgment of the case-detection rate. For some countries, with implausibly large numbers of smear-negative and extra-pulmonary cases notified in individuals younger than 15 years, we have excluded these data from the

analysis. However, the Bayesian meta-regression identifies a solution for incidence that is consistent with prevalence data and estimates of cause-specific mortality. Because this analysis is undertaken using age-specific and sex-specific rates, it also takes into account the changing relations between incidence, prevalence, remission, excess mortality, and cause-specific mortality with age and sex. Because true incidence in any country is not known, our estimates as well as WHO's depend on expert judgment on the case-detection rate. Systematic bias in the estimated case-detection rate, particularly for earlier time periods, will affect not only the volume of estimated tuberculosis cases but also time trends. India accounts for 27·1% (26·3 to 27·9) of global incident cases in 2013; systematic errors in the estimated incidence in India in the 1990s would have a profound effect on global trends. Perhaps more importantly, our assessment of global trends for death are similar to WHO but differ for prevalence and somewhat for incidence. Because total age-sex-specific case notifications reported to WHO for smear-positive pulmonary tuberculosis have continued to increase—by 1·1 million in 2000, 2·3 million in 2005, and 2·5 million in 2012—differences in time trends stem from assumptions about the case-detection rate and, in our study, the incorporation of information from prevalence surveys and all-cause mortality. Table 9 outlines the differences between our tuberculosis estimation strategy and that of WHO.

Malaria burden rose steadily until 2004 and has since decreased. The Global Fund, President's Malaria Initiative, and other bilateral and private initiatives have spent $11·3 billion in DAH from 2000 to 2011. The hypothesis that global action has been an important factor in these declines is highly plausible.[6,110,138-141] The decline in our assessment is driven by the statistical model fitted to the available but sparse verbal autopsy data. Key independent variables in the model that drive this estimated decline are resistance for first-line agents and ITN coverage. Noor and colleagues'[142] assessment of trends in PfPR from 2000 to 2010 indicate that some countries such as Malawi, Zambia, or DR Congo have had substantial scale-up of ITNs with minimal reduction or increases in PfPR. Explanations for the mismatch between ITN scale-up and changes in PfPR could lie in the estimation of any of PfPR, ITNs, or local factors that affect who actually receives and uses ITNs, or it could be a function of other factors—eg, climatic changes over this period. There could also be important threshold or saturation effects for ITNs on PfPR. While the substantial decline in child mortality in the past 5 years is welcome news, understanding the relative role of artemisin in combination treatment scale-up and vector control is challenging and might vary by country. The variability in the relation between ITNs and PfPR at the national level emphasises the risks of simply assuming that ITN scale-up at the national level will yield the percentage reduction in child deaths seen in the randomised trials; a strategy used by Child Health Epidemiology Reference Group (CHERG) in their child mortality estimates. It is also important to note that the CHERG models did not include a first-line drug resistance as a covariate. Our findings show this to be an important predictor in the Africa models in particular and a key driver of the temporal trend noted in this region. Table 10 outlines the differences between our malaria estimation strategy and that of WHO.

MDG6 brought global attention to these three diseases, ushering in an unprecedented focus on specific diseases in the broader development agenda. Despite many who questioned the wisdom of a focus on specific diseases, there has been accelerated progress on HIV, malaria, and tuberculosis since 2000. In the case of HIV, our estimation strategy allows for direct

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quantification of years of life saved, which have been substantial. For tuberculosis and malaria, we see accelerated reductions in deaths and cases compared with the decade before the Millennium Declaration. Rigorously assigning causality to these accelerations to the global collective action catalysed by the Millennium Declaration is beyond the scope of this paper and likely impossible in view of the data limitations. Nevertheless, as governments and the global community debate the nature, scope, and utility of setting new global targets post-2015, these findings should be taken into consideration.

Our comparative analysis of these three diseases shows pronounced differences in data gaps and measurement challenges. Antenatal clinic serosurveillance and population surveys in generalised epidemics have been a powerful tool for tracking evolution of the HIV epidemic with real data collected on an annual basis. Cause of death data in many countries with concentrated epidemics also provide a timely way to examine the effect of HIV. But, national data for the outcome of ART is weak. Measures such as retention in care and loss to follow-up are often incomplete and difficult to compare across facilities, programmes, and countries. UNAIDS and our modelling do not routinely use national data for treatment outcomes and depend on cohort or published studies. In view of the huge effect of ART on death and prevalence, more accurate and continuous monitoring of ART outcomes and costs must be a high priority. By contrast with HIV, tuberculosis treatment outcomes are highly standardised and reported to WHO at least through the end of treatment. However, real-time data for the time-trends of tuberculosis is hard to come by. Case notifications can only be interpreted by resorting to expert opinion on the case detection rate, and prevalence surveys are infrequent and require large sample sizes. A system analogous to the antenatal clinic serosurveillance for tuberculosis would be possible if new diagnostics emerge that can quantitatively assess load of bacilli in an infected individual. Pending such a technological advance, more frequent prevalence surveys and perhaps capture-recapture studies[82] are the only direct measurement available to track evolution of the epidemic. In our study, ARC for incidence and prevalence 2000 to 2013 is correlated (0·93). Information about malaria clinical cases and deaths is much weaker than for HIV or tuberculosis. Case reports are very incomplete. Most deaths occur in places without vital registration systems. Verbal autopsy is widely believed to exaggerate malaria deaths, especially in adults,[143-145] in view of the tendency to overdiagnose malaria in African hospital settings;[146-149] our systematic review of validation studies, though, shows low sensitivity (33%) and low specificity (93%). Bias is a function of both sensitivity and specificity. If these validation studies that are published are correct we might be underestimating and not overestimating malaria deaths in adults and children in areas with substantial malaria and the reverse in areas with little malaria. The only comparatively easy-to-measure outcome related to malaria is the *P falciparum* parasite rate. Local surveys have been usefully collated and analysed by Noor and colleagues and the Malaria Atlas Project.[142] These data provide hard evidence on the trends in a measurable outcome; the challenge is that there is a loose relation in the available data between PfPR and incidence or mortality. In view of how important malaria is, the state of monitoring systems for malaria burden is poor. Repeated verbal autopsy studies combined with carefully designed validation studies would be helpful. Better data for the incidence of clinical episodes confirmed with rapid diagnostic tests and how it varies as a function of the PfPR would improve incidence estimation.

Findings for these three diseases draw attention to the difference between ICD-assigned underlying cause of death and the total mortality attributable to a disease including pathways through which a disease aggravates other disorders. ICD rules treat disorders—not just these three diseases—in this regard in substantially different ways. All deaths directly related to pregnancy and childbirth and any deaths aggravated by pregnancy are counted as maternal deaths. For HIV, all deaths in individuals who are HIV-positive are assigned to HIV unless they are due to completely incidental causes such as a road traffic injury. Following this convention, tuberculosis deaths in HIV-positive people are assigned to HIV not tuberculosis. In the case of malaria, there has long been the recognition that malaria might increase the risk of death in children and adults from other causes such as septicaemia or chronic kidney disease.[150-152] Early studies after the country-by-country elimination or rapid control of malaria documented rapid changes in deaths from pneumonia and chronic kidney disease,[153,154] suggesting the full effects of malaria on mortality are greater than the ICD-coded malaria deaths. The ITN randomised controlled trials based on verbal autopsy documented that about half of the declines in under-5 mortality were in causes other than malaria assigned through a verbal autopsy.[155,156] Our understanding of the magnitude of each disease is affected by the at-times arbitrary rules governing assigning causes of death.

There are two important general observations from our analysis of HIV compared with prior analyses that might be relevant to other diseases. First, we saw that concentrated epidemics have been systematically over estimated by a factor on average of more than two. Overestimation is most likely related to a tendency to overestimate the size of high-risk groups for which little information exists. Why would expert judgment be, on average, so wrong? The disconnect in many countries between expert judgment and the results emerging from the analysis of cause of death data should caution researchers in the future from too much dependence on expert judgment in descriptive epidemiology. Second, we saw a systematic under-estimation of uncertainty in many countries in the UNAIDS analysis. Their assessment for South Africa, for example, had for 2010 an uncertainty interval with a coefficient of variation of 0·03. Our assessment before matching on all-cause mortality had a coefficient of variation about six times higher (0·19) in the same year. There is a general tendency, we believe, in many modelling efforts to underestimate uncertainty when arbitrary assumptions about parameters are made. For example, the default assumptions for uncertainty in the UNAIDS Spectrum model is a coefficient of variation 0·05 for mortality on and off ART. We find from our empirical analysis coefficients of variation that range from 0·44 (in the age group 15–24 years and CD4 count greater than 500) to 1·00 (in people aged 45 years or older and a CD4 count greater than 500). In other words, uncertainty in these parameters seems to have been underestimated, with the real value approximately ten times larger. This is not a critique of the UNAIDS Spectrum modelling effort, rather a reminder that statistical analysis of parameter uncertainty often shows that we know much less than we think.

Our analysis of HIV in India based on the 2005–06 National Family Health Survey and antenatal clinic serosurveillance suggests that in 2002 there were 287 000 (199 000 to 377 000) deaths. Cause of death data, however, are available from several sources all pointing to substantially lower numbers of deaths than UNAIDS high-risk group analysis. Using data for 2001–03, investigators in the Million Death Study reported an estimated 59 000–140 000

deaths in 2004. The urban Medical Certification of Causes of Death system recorded a peak age-standardised death rate in 6·3 per 100 000 population, which is equivalent at the national level to 57 000 deaths. We did not use these sources in our assessment; the substantial mismatch between our estimates draws attention to the need for improved understanding of causes of death in India.

Some global health efforts to develop robust estimates of the burden of disease sometimes end up using both empirical measurement on incidence, prevalence, and cause-specific mortality plus coverage of interventions and assumed effectiveness of interventions. The blending of real measurement of outcome and assumed mapping of interventions to outcome is justified because recent scale-up of interventions might not be accounted for in the sparse measurements that are available. We used the modified Spectrum model to map ART coverage into likely changes in mortality from HIV. These findings are lent support in some countries by measured declines in all-cause mortality or cause-specific mortality but in other countries are based entirely on the presumed relation between intervention roll-out and mortality. Many examples of such blending of data for outcome and intervention coverage exist: CHERG estimates of decreases in child deaths due to ITNs and *Hemophilus influenza* type B vaccine coverage are not based on any statistical relation but on the assumption that interventions will yield the decreases seen in randomised trials. These are reasonable assumptions but fundamental difference exist between observing the change in outcome as opposed to assuming the outcome has changed; this difference is not immediately evident in global health estimation efforts. It can yield circular analyses in which estimates are used by other authors to assess impact. In general, in the GBD 2013, we have sought to use largely empirical data and statistical associations seen in the data to make estimates. But for HIV in particular, we have used the approach embodied in Spectrum.

This analysis of data for HIV, tuberculosis, and malaria has many limitations in view of the ambition to track incidence, prevalence, and mortality for 188 countries from 1990 to 2013. First, ART estimates for 2013 are highly preliminary. Countries have reported ART scale-up through 2012 and provided estimates for 2013. Many of these estimates were aspirational and we have used growth rates over the 5 years 2008–12 to adjust these 2013 estimates. Second, we have not independently validated the country reports of ART scale-up. We have added to the uncertainty by randomly varying ART scale-up by sampling a uniform distribution from plus to minus 10% but this presumes that, on average, ART scale-up is not exaggerated. Third, we have used 102 studies of ART outcomes to inform our assumptions of death rates on ART. There was much variation across sites. More recent programmes might be achieving better outcomes than previous studies have shown if there has been shared learning across programmes. Available studies might also be biased towards better outcomes through the publication bias; poor programmes are unlikely to seek to publish their results. There was insufficient national data to use local information about each country on ART programmes. Our estimates might be biased up or down for a given country because local ART outcomes might be better or worse than the sub-Saharan Africa average. Future rounds of estimation will be substantially improved by more robust ART treatment outcome data obtained from nationally representative samples of patients on ART across a wider range of countries. Fourth, we have sought to find epidemic curves for the major

generalised epidemics that are both consistent with available prevalence data and all-cause mortality data derived from sources such as vital registration or sibling histories in household surveys. The process of matching all-cause mortality draws and Spectrum outputs that are consistent also substantially reduces uncertainty. In view of the mismatch of these data sources, we are probably underestimating uncertainty in these countries. Fifth, we have not modified the UNAIDS assumptions for survival in children infected with HIV. However, published studies from high-income countries pre-ART suggest much higher survival.[157] Our estimates of death in the age-groups 5–9 years and 10–14 years might therefore be exaggerated. Sixth, our estimates of uncertainty for HIV could be underestimated because some of our uncertainty ranges for parameter inputs have been selected arbitrarily and true variation, for example, in age-sex patterns of incidence might be larger. The idea that variations in age-sex patterns of incidence might be larger is lent support by the number of age-sex-country-years in which our estimates of prevalence are different to those available from national prevalence surveys. Seventh, on the basis of debate over the burden of malaria in adults, we chose not to redistribute garbage code deaths onto malaria in verbal autopsy studies in adults, which led to a reduction in the estimated number of adult malaria deaths. Although this choice was informed by expert opinion, it was not based on any direct data. Even without the redistribution of garbage codes, the percentage of deaths occurring in adults in Africa is still high and has to be interpreted with caution in view of the potential for misclassification bias in verbal autopsies. Alternatively, the choice not to redistribute ill-defined codes onto malaria might bias our adult deaths downwards. Eighth, Noor and colleagues have published PfPR for 2000 and 2010.[142] A full time-series of PfPR would be a useful covariate for modelling the burden of malaria. The Malaria Atlas Project is working on such time-series analysis of PfPR and when it is finalised it would strengthen the analysis of malaria trends. Ninth, our uncertainty intervals for malaria incidence and mortality incorporate sampling uncertainty, non-sampling un certainty, and model-specification uncertainty, but do not incorporate the uncertainty that can stem from misclassification biases in verbal autopsy. Uncertainty is probably underestimated due to the limitations of verbal autopsy for malaria in children and adults. Tenth, findings from other studies in countries such as The Gambia suggest substantial decreases in malaria in these settings; in our analysis of mortality, however, these types of studies have not been used.[158,159] Eleventh, our analysis of tuberculosis assumes that local expert judgment about the case-detection rate is unbiased; this assumption, however, might be incorrect for countries with higher or lower case-detection rates. Twelfth, our uncertainty intervals for tuberculosis incidence and prevalence generated from DisMod-MR 2.0 are probably underestimated. The intervals are narrow because we have extensive data inputs for essentially all countries in the form of adjusted case-notifications and CODEm estimates of all-cause mortality. Although each data point has substantial uncertainty, the meta-regression produces narrow estimates of the predicted mean value for an age-sex-country-year because of the extensive and often consistent data. These intervals do not capture the potential for systematic error in some of the data-processing steps such as the use of the expert-based case-detection rate. Despite these important limitations, the GBD approach has many advantages, primarily because it is a comprehensive and clearly documented approach to disease burden estimation that examines all the available data and invests substantial

effort into standardisation of definitions, data adjustments, and modelling across all diseases and injuries.

The focus of the global health community on action to reduce HIV/AIDS, tuberculosis, and malaria, enshrined in MDG6, was not only appropriate in 2000 at the Millennium Declaration, but is increasingly relevant now in view of the slow but important progress that disease control strategies have yielded, particularly since 2005. Much remains to be done, however: although evidence now exists that the implementation of known interventions is beginning to have an effect, it is probably less than is widely believed, or hoped. But these interventions are working, and need to be rapidly scaled up with more funding, more emphasis on national health system strengthening in key affected countries to increase access to them by the poor, and more targeted research to accelerate progress. What is also clear from this analysis as we enter the final phase of the MDG era is how little we reliably know in many countries to track progress. Rapidly reducing the massive uncertainty that surrounds the measurement of these diseases, particularly malaria, will be essential if we are to better monitor, and respond to, evidence about progress, or not, with their control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Lancet. Author manuscript; available in PMC 2014 October 20.

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