Monitoring progress towards Millennium Development Goal 4 in generalised HIV epidemics: measurement and correction for bias in child mortality statistics

Simon Gregson*, Timothy B Hallett*, Felicia Kurwa, Geoffrey P Garnett, Sabada Dube, Godwin Chawira, Peter R Mason, Constance A Nyamukapa

* These authors contributed equally to this work.

Introduction

Millennium Development Goal 4 (MDG4) requires that countries reduce child mortality rates by 2/3rds between 1990 and 2015 (1). To establish whether MDG4 is met, improved methods are being developed to measure trends in child mortality, which are usually assessed by interviewing mothers about the survival of their children (2-4). However, limited headway has been made in addressing an important potential bias in estimates of infant and under-5 mortality rates in populations subject to generalised HIV epidemics (2) that could lead to incorrect conclusions being drawn on progress towards MDG4. This would arise if mortality was highest in children born to women infected with HIV when these women are subsequently less likely to be included in surveys because they are ill or have died. The magnitude of this bias is hard to predict because it is determined by a set of inter-dependent relationships between fertility, mother's age, stage of HIV infection, chance of mother-to-child transmission and survival of infected children.

We use data on mortality rates amongst children born to both living and deceased women from a prospective population-based cohort study in Zimbabwe to test the hypothesis that the correlation between maternal and early child HIV infection and death can cause a bias in child mortality rate estimates in excess of 5% and develop a mathematical model to produce estimates of the bias in national surveys in countries with generalised epidemics.

Methods

Empirical data and data analysis methods

The data were taken from the Manicaland HIV/STD Prevention Study in eastern Zimbabwe (5). We conducted a baseline census of households in 12 locations in a phased manner between July 1998 and February 2000. A random sample of adult household residents was recruited into an open cohort. Second and third rounds of censuses and surveys were conducted 3 years and 5 years after baseline, respectively. The questionnaires administered to members of the open cohort at each round included sections on fertility histories and child survival similar to those collected in Demographic and Health Surveys (DHS) (6). At each round, verbal autopsy interviews were conducted with caregivers of cohort members who had died since the previous round (7), in which data were collected on births between the date of last interview and the date of death and on child mortality among these and earlier births.

Standard estimates (6) of infant and under-5 mortality rates were calculated for children born to surviving women aged 15-49 years from the fertility history data collected from women interviewed in the third round of the survey. To measure the bias in estimates arising from correlation between maternal and early child mortality, analogous calculations were done for the children of deceased women using the verbal autopsy interview data from rounds 2 and 3. To obtain corrected statistics for infant and under-5 mortality rates, the estimates for children born to surviving and deceased women were combined, adjusting for the sampling of women in the open cohort and loss-to-follow-up amongst women who died.

Model structure and analysis

An individual-based stochastic model was created to simulate the mortality and fertility experiences of cohorts of women born in rural Zimbabwe between 1920 and 2005 and the mortality experience of their children. Parametric probability distributions were used to describe the relationships between age, fertility, chance of HIV infection, time since HIV infection, HIV-related sub-fertility, AIDS-related and background mortality rates. The life-course experiences of women were simulated by drawing randomly from these distributions. The model outputs a dataset analogous to that obtained in a cross-sectional survey of fertility histories. Model input settings for the rural Zimbabwe application were based on data from the Manicaland study and national reports, and a sensitivity analysis was performed to explore the sensitivity of model outcomes to these assumptions.

Using the data generated by the mathematical model, we produced 3 sets of time-series of infant and under-5 mortality measurements for Zimbabwe. The first, the 'DHS analogue', was created using the standard DHS methods (6). These estimates were compared with reported national estimates for Zimbabwe from the 1988, 1994, 1999 and 2005 DHS surveys to test the validity of the model (8-11). The second, the 'DHS continuous' time series, estimated mortality in a similar way,

but with estimates being calculated on a continuous basis and without censoring of child survival times. Finally, the 'Corrected' time-series was calculated like the DHS continuous time-series, except that it also included reports for women who died of AIDS before the survey. The results from the DHS continuous and corrected time-series were compared and differences between the two series were taken as estimates for the extent of under-estimation in mortality rates expected to occur in routine statistics derived from cross-sectional surveys in rural Zimbabwe during the HIV epidemic. For further model validation, the expected differences in the late 1990s/early 2000s were compared with the empirical estimates from Manicaland.

A scenario-based sensitivity analysis was conducted to identify the main determinants of the extent of bias. The model was used to estimate the impact of hypothetical PMTCT and adult anti-retroviral therapy (ART) interventions on infant and under-5 mortality.

Results

Empirical quantification of bias in child mortality rates in Manicaland, Zimbabwe

The empirical estimates are summarised in Table 1. In round 3 of the Manicaland survey, complete fertility histories with child mortality data were collected for 6,236 women aged 15-49 years, who reported a total of 3,308 live births in the preceding 5 years. These data yielded uncorrected estimates of infant and under-5 mortality of 45.9 and 67.1 per thousand live births, respectively. For children born to women who were HIV positive at round 3, the infant and under-5 mortality rates were 85.7 and 135.3 per thousand, respectively. For children born to uninfected women, the corresponding rates were 32.3 and 46.3 per thousand.

	Surviving mothers	Deceased mothers	All mothers	Under-estimate
	(/000)	(/000)	(/000)	(%)
Infant mortality rate	45.9	146.8	48.9	6.7
Under-five mortality rate	67.1	283.8	73.7	9.8
Number of births in last 5 years†	5 325	167	5 492	-
Number of women aged 15-49 years, 2003-05	10 315	1 253	-	-

† In the 5 years before the most recent survey round (conducted July 2003 to August 2005)

Table 1: **Empirical estimates of infant and child mortality and their under-assessment in cross-sectional surveys due to HIV-related maternal mortality from a prospective cohort in Manicaland, Zimbabwe, 1998-2005. The under-estimate is the difference between the mortality rates for children born to all mothers and for children born to surviving mothers, expressed as a percentage of the mortality rate for children born to surviving mothers.**

A total of 350 female members of the cohort, who would have been aged between 15 and 49 years at last birthday at round 3, were recorded as having died within the combined 5-year inter-survey period. Fertility histories were available from individual and verbal autopsy interviews for 322 (89.4%) of these women, who were reported to have had 43 live births in the 5 years before the round 3 interviews and a further 80 live births in the preceding 5 years. These children experienced infant and under-5 mortality rates of 146.8 and 283.8 per thousand, respectively. In total, 10,315 women aged 15-49 years were enumerated in the household census in round 3. If these women experienced similar birth rates over the previous 5 years to those from whom fertility histories were obtained, they would have had a total of 5,325 live births. Furthermore, assuming that women who died between the first and third rounds of the survey were lost to follow-up (due to reasons other than death) at the same rates as women who survived, a total of 1,253 women would have died during this period. Again, if these deceased women experienced the same birth rates as the 322 for whom fertility histories were collected, they would have given birth to a total of 167 children. Applying the infant and under-5 mortality rates observed in children born to surviving and deceased women to these estimates of the numbers of babies born to surviving and deceased women during the 5 year inter-survey period yields corrected estimates of infant and under-5 mortality of 48.9 per thousand and 73.7 per thousand, respectively. Comparing the corrected and uncorrected statistics indicates that the standard cross-sectional survey estimates under-state true levels of infant and under-5 mortality by 6.7% and 9.8%, respectively, of their observed values.

Model estimates of bias over time in Zimbabwe and other selected countries in Africa

Parameterised for rural Zimbabwe, the model generates a DHS analogue time-series that is in substantial qualitative agreement with that observed in the national DHS surveys. The 3 mortality measures all show marked increases in mortality in the period 1990-2005, largely reversing reductions during the 1980s (Fig. 1). Mortality is expected to decrease after 2005 due to declines in HIV prevalence in adults since 2000 (14). In the pre-AIDS era, the DHS analogue estimates for 0-4, 5-9 and 10-14 years before the survey are in line with the continuous measurements. However, the DHS analogous estimates from the 2005 survey for mortality in 5-9 and 10-14 years before the survey are lower than the continuous measurement. This pattern is reflected in the DHS data for Zimbabwe. It arises because the women who report having children during these earlier periods are disproportionately women who are either uninfected now or who have become infected recently.

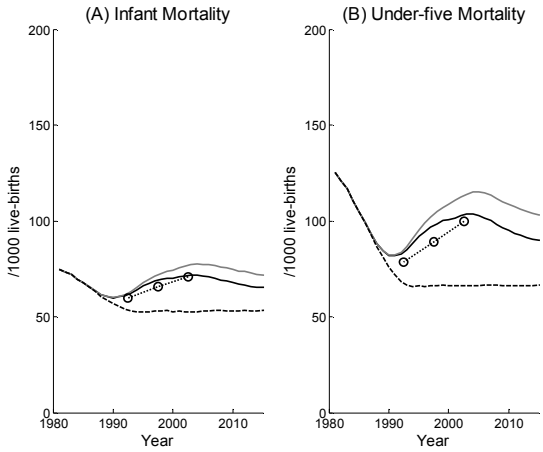

Figure 1: Modelled trend in (A) infant, and (B) under-5 mortality, 1980-2015. Black dashed lines show mortality rates in the absence of the HIV epidemic; black solid lines show the *DHS continuous* time-series; grey lines show the *corrected* time-series, accounting for HIV-related deaths among women; circle points show the *DHS analogue rates* that would be estimated in a 2005 cross-sectional survey for periods 0-4, 5-9 & 10-14 years before the survey. No PMTCT intervention is included.

The corrected time-series is substantially greater than the DHS analogue and DHS continuous measurements. The magnitude of the bias in rural Zimbabwe, from 1980-2015, together with the empirical results from Manicaland, is shown in Figure 2. The extent of the bias grows in the wake of the HIV epidemic – the effect is minimal before the early 1990s but exceeds 5% by the late 1990s. The extent of the bias is greater for under-5 mortality than for infant mortality because mothers who gave birth further into the past are more likely to have died before the interview date. The empirical results for 1998-2005 agree well with the model, which indicates under-estimates for infant and under-5 mortality for this period of 7.1% and 9.7%, respectively.

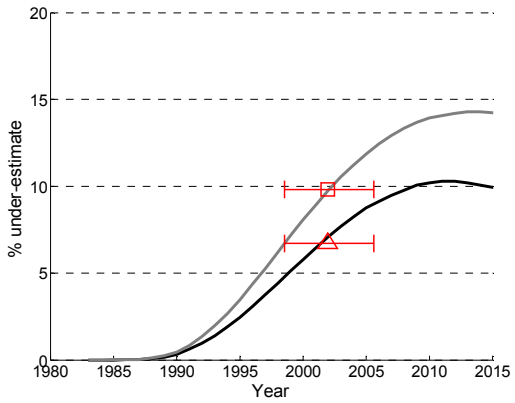

Figure 2: The under-estimate in infant (black line) and under-5 (grey line) mortality, 1980-2015, predicted by the model. The triangle and the square show, respectively, the empirical results for infant and under-5 mortality from Table 1 (the horizontal whiskers show the period of the survey [1998-2005] and the symbol is at the midpoint [2002]). No intervention to prevent mother-to-child transmission is included.

For the 5-year period 2005-9, the model predicts that infant mortality and under-5 mortality could be under-estimated by 9% and 13%, respectively. Lower background childhood mortality leads to greater biases, since the fraction of HIV-related deaths among children is higher. Higher fertility at older ages leads to greater biases, caused by the greater number of births to late- stage infected mothers at older ages. The impact of interventions reducing background rates of mortality for children may be over-estimated in standard statistics compared to corrected statistics (Fig. 3a) because the contribution of HIV, which remains at a high level despite the intervention, is under-represented in the uncorrected statistics. In contrast, the full impact of PMTCT (and adult ART) interventions, which directly reduce HIV-related mortality among children, will not be recorded in standard mortality statistics (Fig 3b), since HIV-related deaths are under-counted at baseline.

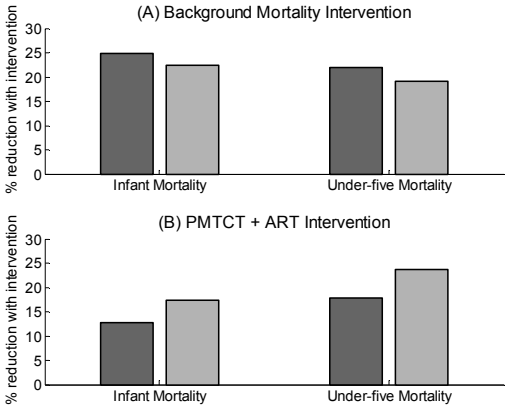

Figure 3: Estimates of the impact on infant and under-5 mortality of interventions to: (A) reduce background mortality by 30%, or (B) prevent mother-to-child transmission (PMTCT). The PMTCT intervention provides for all women after the year 2000 to access therapy that reduces the chance of mother-to-child transmission by 50%, and for 50% of women eligible for ART after year 2003 to be treated. The bars show the relative mortality rate in 2015 (intervention scenario versus no intervention scenario) as recorded in the DHS continuous time-series (dark grey), and the corresponding measurement for the corrected time-series, accounting for HIV-related deaths among women (light grey).

Discussion

We used direct empirical and mathematical modelling methods to measure and evaluate the extent of bias, due to correlation between maternal and child AIDS mortality, on levels and trends in early child mortality statistics derived by applying standard methods to data from retrospective fertility histories collected in household surveys. Ward and Zaba proposed an adjustment to the indirect "children surviving / children ever born" method for estimating child mortality to account for correlation between maternal and child mortality (12). However, as far as we are aware, the bias resulting from the more direct approach based on fertility histories examined here has not previously been evaluated (6).

The data from Zimbabwe are based on a relatively small sample of children born to women who died but nevertheless provide empirical evidence that this bias can be substantial, with under-estimation of both infant and under-5 mortality exceeding 5%, in a population in which HIV prevalence fell from 23% to 18% over the period 1998-2005 (13) when female adult mortality was 26/1000 (with 74% of deaths being associated with HIV infection (15)) and PMTCT uptake was minimal (16). Using a specially-developed mathematical model, we demonstrated that the bias will vary between countries according to size and stage of HIV epidemic and level of background mortality. Furthermore, the bias will typically be greater in estimates made for periods further removed in time from the survey date. The model results also show how the bias will generally increase in growing and stable epidemics, hampering comparison between countries with different stage epidemics. Reductions in background mortality may be over-estimated, whilst the effect of PMTCT programmes introduced in the early 2000s in reducing mortality will be substantially under-estimated unless the bias is corrected for.

These findings show that standard infant and under-5 mortality statistics need to be corrected for bias due to correlation between maternal and early childhood mortality in populations with generalised HIV epidemics. This will be particularly important when measuring trends, evaluating the impact of PMTCT programmes, or assessing progress towards MDG4.

References

1. United Nations Millennium Declaration. 55/2. United Nations General Assembly; 2000. 9.
2. UNICEF, WHO, The World Bank, Division UP. Levels and trends of child mortality in 2006: estimates developed by the Inter-agency Group for Child Mortality Estimation New York: UNICEF; 2007.
3. Countdown Coverage Writing Group on behalf of the Countdown to 2015 Core Group. Countdown to 2015 for maternal, newborn, and child survival: the 2008 report on tracking coverage of interventions. The Lancet. 2008; 371(9620): 1247-58.
4. Murray CJL, Laakso T, Shibuya K, Hill K, Lopez AD. Can we achieve the Millennium Development Goal 4? New analyses of country trends and forecasts of under-5 mortality to 2015. The Lancet. 2007; 370(9592): 1040-54.
5. Gregson S, Garnett GP, Nyamukapa CA, Hallett TB, Lewis JJC, Mason PR, et al. HIV decline associated with behaviour change in eastern Zimbabwe. Science. 2006;311(3 February 2006): 664-6.
6. Rutstein SO, Rojas G. Guide to DHS Statistics. Calverton, Maryland: Demographic and Health Surveys, ORC Macro; 2006.
7. Lopman BA, Barnabas RV, Boerma JT, Chawira G, Gaitskell K, Harrop T, et al. Creating and validating an algorithm to measure AIDS mortality in the adult population using verbal autopsy Public Library of Science Medicine. 2006; 3(8): 1273-81.
8. Zimbabwe Central Statistical Office. Zimbabwe Demographic and Health Survey, 1988. Harare: Zimbabwe Central Statistical Office and Macro International; 1989.
9. Zimbabwe Central Statistical Office. Zimbabwe Demographic and Health Survey, 1999. Harare: Zimbabwe Central Statistical Office and Macro International; 2000.
10. Zimbabwe Central Statistical Office. Zimbabwe Demographic and Health Survey, 2005-2006. Harare: Zimbabwe Central Statistical Office and Macro International; 2007.
11. Zimbabwe Central Statistical Office. Zimbabwe Demographic Health Survey, 1994: Zimbabwe Central Statistical Office; 1995.
12. Ward P, Zaba B. The effect of HIV on the estimation of child mortality using the children surviving / children ever born technique. London: London School of Hygiene and Tropical Medicine Undated. p.30.
13. Gregson S, Nyamukapa CA, Lopman B, Mushati P, Garnett GP, Chandiwana SK, et al. A critique of early models of the demographic impact of HIV/AIDS in sub-Saharan Africa based on empirical data from Zimbabwe. Proceedings of the National Academy of Sciences. 2007; 104(37): 14586-91.
14. UNAIDS. Evidence for HIV Decline in Zimbabwe: A Comprehensive Review of the Epidemiological Data. Geneva: UNAIDS; 2005.
15. Smith J, Mushati P, Kurwa F, Mason PR, Gregson S, Lopman B. Changing patterns of adult mortality as the HIV epidemic matures in Manicaland, eastern Zimbabwe. AIDS. 2007; 21(Supplement): S81-S6.
16. Dube S, Boily M-C, Mugurungi O, Mahomva A, Chikhata F, Gregson S. Estimating vertically acquired HIV infections and the impact of the prevention of mother-to-child transmission program in Zimbabwe: insights from decision analysis models. Journal of Acquired Immune Deficiency Syndromes. 2008; 48(1):72-81.