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CHILD SURVIVAL BY HIV STATUS OF THE MOTHER: EVIDENCE FROM DHS AND AIS SURVEYS

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Child Survival by HIV Status of the Mother: Evidence from DHS and AIS Surveys

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Preface

The Demographic and Health Surveys (DHS) Program is one of the principal sources of international data on fertility, family planning, maternal and child health, nutrition, mortality, environmental health, HIV/AIDS, malaria, and provision of health services.

One of the objectives of The DHS Program is to provide policymakers and program managers in low- and middle-income countries with easily accessible data on levels and trends for a wide range of health and demographic indicators. DHS Comparative Reports provide such information, usually for a large number of countries in each report. These reports are largely descriptive, without multivariate methods, but when possible they include confidence intervals and/or statistical tests.

The topics in the DHS Comparative Reports series are selected by The DHS Program in consultation with the U.S. Agency for International Development.

It is hoped that the DHS Comparative Reports will be useful to researchers, policymakers, and survey specialists, particularly those engaged in work in low- and middle-income countries.

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Abstract

Mother-to-child transmission of HIV is the predominant cause of HIV infection in children. In the absence of treatment, children infected with HIV experience higher mortality rates than their HIV-negative counterparts. However, rapidly expanding programs for the elimination of mother-to-child transmission hold promise for greatly reducing the number of new pediatric HIV infections and improving the survival of children of HIV-positive women.

This report presents the results of a bivariate analysis of data from 20 surveys in 13 countries conducted under the DHS Program between 2003 and 2012 in order to compare the levels of child mortality among children of HIV-positive and HIV-negative women, and to explore changes over time. Across all surveys in the analysis, children of HIV-positive women generally experience higher mortality rates than children of HIV-negative women. In 17 of 20 surveys studied, children of HIV-positive women have significantly higher under-five mortality rates than children of HIV-negative women. The relative risks range from 1.5 in the 2011 Cameroon DHS to 3.6 in the 2006 Swaziland DHS. The results show little evidence of improvement in the survival of children of HIV-positive women compared with children of HIV-negative women over time.

Executive Summary

Mother-to-child transmission of HIV is the predominant cause of HIV infection in children. In the absence of treatment, children infected with HIV experience much higher mortality rates than their HIV-negative counterparts. However, rapidly expanding programs for the elimination of mother-to-child transmission (EMTCT) hold promise for greatly reducing the number of new pediatric HIV infections and improving the survival of children of HIV-positive women.

This report analyses data from 20 surveys in 13 countries conducted under the DHS Program in order to compare the levels of child mortality among children of HIV-positive and HIV-negative women, and to explore changes over time. The child mortality rates are calculated from information gathered in the birth history in the woman's interview, while the woman's current HIV status is taken from an HIV test conducted as part of the surveys. The analysis consists of bivariate associations between child mortality and maternal HIV status for each individual survey. Mortality rates are presented for children of HIV-positive women, children of HIV-negative women, and all children combined. The analysis also calculates unadjusted relative risks to measure the probability of dying among children of HIV-positive women compared with the probability of dying among children of HIV-negative women.

Across all surveys in the analysis, children of HIV-positive women generally experience higher mortality rates than children of HIV-negative women. In 17 of 20 surveys studied, children of HIV-positive women have significantly higher under-five mortality rates than children of HIV-negative women. These relative risks range from 1.5 in the 2011 Cameroon DHS to 3.6 in the 2006 Swaziland DHS. The greater risk of death among children of HIV-positive mothers compared with those of HIV-negative mothers is observed for all age groups, except during the neonatal period during which the mortality rates for children of HIV-positive and HIV-negative women are similar. The postneonatal period (1-12 months) appears to be the period during which children of HIV-positive women experience the greatest increased risk of mortality, with children of HIV-positive women being 3.2 times as likely to die as children of HIV-negative women, according to the average relative risk across all 20 surveys.

To examine change over time, the analysis compared the mortality rates of children of HIV-positive and HIV-negative women in seven countries with two successive surveys. The results show little evidence of improvement in the survival of children of HIV-positive women compared with children of HIV-negative women in these countries over time. However, it is important note that due to the timing of data collection and the length of the reference periods for the surveys, many of the children in the analysis may have been exposed to HIV at a time when coverage of EMTCT interventions and anti-retroviral therapy was much lower than current levels, and when the interventions available, such as single-dose nevirapine, were less effective than those currently recommended. If the current goal of virtually eliminating new HIV infections in children is achieved and sustained for several years, population-based surveys will reflect the impact with diminishing differences between the mortality rates of children of HIV-positive and HIV-negative women.

1. Introduction

In 2012, an estimated 260,000 children became newly infected with HIV/AIDS (UNAIDS 2013). In the absence of treatment, children infected with HIV experience high mortality rates, with some studies estimating that 35-59 percent of children infected with HIV die before reaching age 2 (Kourtis et al. 2006). Over 90 percent of children living with HIV are believed to have been infected through mother-to-child transmission (MTCT) (WHO 2010a). The risk of MTCT can be greatly reduced through programs for the elimination of mother-to-child transmission (EMTCT), which include antiretroviral (ARV) medications for the mother and newborn, among other components. The coverage of national EMTCT programs has expanded rapidly since they began in the mid-2000s, but many women and newborns remain uncovered. Furthermore, women still receive drug regimens that are not in line with—and are less effective than—the latest recommendations (UNAIDS 2011). In addition to high mortality among children infected with HIV, uninfected children of HIV-positive mothers may also experience higher mortality than children of HIV-negative mothers. For all of these reasons, children of HIV-positive women are expected to experience higher mortality, on average, than children of HIV-negative women.

This analysis attempts to answer three questions:

1. Do surveys conducted by the Demographic and Health Surveys (DHS) Program provide evidence that children of HIV-positive women experience higher mortality rates than children of HIV-negative women?
2. Does the excess risk of mortality differ by age of the child?
3. Do the surveys provide evidence of improvement over time in the mortality of children of HIV-positive women, either in absolute terms or relative to the mortality of children of HIV-negative mothers?

The survival of children of HIV-positive women has been measured in cohort studies and clinical trials, but little analysis has been done using the data available from nationally representative population-based surveys. A number of surveys conducted as part of the DHS Program include both HIV testing and a birth history in the woman's interview. It is possible to use these data to calculate past child mortality rates by the current HIV status of the mother. The HIV status of the children themselves is not available, nor is the HIV status of the mother at the time the child was born.

This report analyses data from 20 surveys in 13 countries conducted under the DHS Program in order to compare the levels of child mortality among children of HIV-positive and HIV-negative women, and to explore changes over time. Data are presented by the traditional component rates of child mortality—neonatal, postneonatal, infant, child, and under-five mortality—in order to assess differences by age in the mortality rates of children of HIV-positive and HIV-negative women.

2. Background

The data presented in this report were collected in the context of rapid evolution and expansion of EMTCT programs. In order to interpret what the mortality rates from this analysis may indicate about the effectiveness of these interventions, it is important first to take into consideration several key pieces of information:

(1) What is the likelihood that a child born to an HIV-positive mother will acquire HIV, in the absence of intervention?

(2) What are the mortality rates for children infected with HIV?

(3) What standards of care were in place during the reference periods for these surveys, how effective are these standards of care, and what percentage of women and children were exposed to them?

This section provides background information relevant to these questions. The section then summarizes the data available from clinical trials and cohort studies on the mortality rates of children of HIV-positive and HIV-negative women. Finally, the section applies the key conclusions from the literature to the current analysis and discusses some additional considerations that must be made when interpreting the mortality data from the surveys included in this report.

2.1. MTCT Rates and Timing of Transmission

There is no consensus on the exact probability of transmission of HIV from mother to child, and evidence indicates that transmission rates vary across populations. HIV can be transmitted from mother to child during pregnancy, during delivery, or during breastfeeding. Estimates for the risk of MTCT in breastfeeding populations in the absence of medical intervention generally range from 25 to 45 percent, meaning that 25 to 45 percent of children born to HIV-positive mothers acquire HIV (de Cock et al. 2000).

To estimate the probability of transmission at various stages from early pregnancy through childbirth, Kourtis and colleagues compared the effectiveness of different EMTCT regimens tested in clinical trials (Kourtis et al. 2006). Assuming an overall risk of MTCT with no medical intervention and no breastfeeding of 25 percent, they estimate that 5 percent of children become infected with HIV during the first eight months of pregnancy, 12 percent become infected during the last month of pregnancy, and 8 percent become infected around the time of delivery.

Breastfeeding duration is a principal determinant of the overall risk of transmission. Several studies have suggested that in the absence of treatment, breastfeeding for up to two years increases the cumulative risk of HIV transmission by roughly 10-20 percentage points (Fawzi et al. 2002; Miotti et al. 1999; Nduati et al. 2000; BHITS 2004; Dunn 1992), and accounts for around 40 percent of all HIV infections acquired through MTCT (Kourtis et al. 2006; Nduati et al. 2000).

2.2. Mortality Rates for Children with HIV

Mortality rates among children infected with HIV depend on background all-cause mortality, but evidence consistently shows that children infected with HIV experience higher mortality rates compared with HIV-negative children. In the European Collaborative Study (ECS), a prospective observational study to describe the natural history of HIV in children who acquired the infection from their mothers, 10 percent of children died by age 1, and 28 percent died by age 5 (ECS 1994).

Studies of HIV-infected children in Africa have found higher mortality rates than in Europe. In African settings, it is anticipated that around half of children who acquire HIV from their mothers will die before their second birthday (WHO 2010a). According to a pooled analysis of data from seven randomized MTCT trials in African countries, the risk of death by age 2 was about nine times higher among infected children than among uninfected children. An estimated 35 percent of infected children will die during the first year of life, and an estimated 53 percent of infected children will die by age 2 (Newell et al. 2004a). An observational study of children born to HIV-positive mothers in Rwanda found that the cumulative risk of death among infected children was 26 percent by age 1, 45 percent by age 2, and 62 percent by age 5. By contrast, the cumulative risk of death at age 5 among uninfected children was only 4 percent (Spira et al. 1999).

Other studies in Africa have also found similar differences in the cumulative mortality rates of infected and uninfected children of HIV-positive mothers (Dabis et al. 2001; Brahmbhatt et al. 2006). In short, there is strong evidence that HIV-positive children are at higher risk of death than their HIV-negative counterparts. At the same time, many HIV-positive children survive to reach age 2, age 5, and beyond, even in the absence of antiretroviral therapy (ART).

Data from the ECS and French Pediatric HIV Infection Study indicate that around 20 percent of HIV-positive children progress to serious illness or death during the first year of life, followed by only around 5 percent of children per year in years two through five (Stéphane et al. 1997). This rapid progression of HIV in some children may be associated with earlier age at infection. Evidence suggests that mortality is higher among children infected earlier in life or during pregnancy than among those infected later (Spira et al. 1999; Dabis et al. 2001; Marinda et al. 2007; Newell et al. 2004a; Newell et al. 2004b; Zijenah et al. 2004). Furthermore, children infected during breastfeeding may live for several months before becoming infected and experiencing any increased risk of HIV-related mortality (Newell at el. 2004a). Though the prospective data for children up to age 5 is limited, these findings suggest that much of the higher mortality experienced by HIV-positive children may be accumulated during the first year or two of life.

2.3. Interventions to Reduce MTCT and Promote the Survival of Children Living with HIV

Elimination of MTCT involves multiple program elements, ranging from primary prevention of HIV infection among women of reproductive age, to prevention of unwanted pregnancies among women living with HIV, and to ART for women and their children (UNAIDS 2011).

There is a substantial body of evidence from numerous clinical trials on the effectiveness of various drug regimens for the prevention of MTCT. The first such trial, PACTG 076, involved giving women a short course of zidovudine, an antiretroviral medication, during pregnancy and delivery, followed by zidovudine for the newborn for six weeks. The rate of MTCT in the experimental group was 8 percent, a two-thirds reduction from the 26 percent observed in the comparison group, which received no intervention (Connor et al. 1994).

Though effective, this regimen initially was not feasible in low-resource settings. Less intensive regimens were pursued, including in the HIVNET 012 trial in Uganda. This trial involved a single dose of

nevirapine for the mother at the onset of labor and a single dose of nevirapine for the newborn within the first 72 hours. The rate of MTCT was 16 percent by 18 months (Guay et al. 1999; Jackson et al. 2003). This regimen was adopted in many low-resource settings due to its affordability and ease of administration (Kourtis et al. 2006). The single-dose nevirapine regimen also has its disadvantages, including sub-optimal efficacy and an association with drug resistance in both mothers and children (Abrams 2004). By contrast, ART during pregnancy and childbirth, with no breastfeeding, has been found to prevent nearly all cases of MTCT (Cooper et al. 2002).

In African settings, increased risk of mortality has been associated with replacing breastfeeding with formula feeding (Thior 2006; Kagaayi et al. 2008), and with early and abrupt cessation of breastfeeding (Kuhn et al. 2008). Current recommendations call for breastfeeding and use of ART throughout the entire period that the child is at risk of acquiring HIV through breast milk (WHO 2013).

As a reflection of the rapid advancement in this field, the World Health Organization (WHO) has issued four revisions in its EMTCT recommendations over the past decade. A brief review of these guidelines helps to understand what national policies may have been in place during the reference periods for the surveys in this analysis. (Issues pertaining to the reference period are discussed in greater detail in the following section, "DHS data in context".) None of the WHO guidelines have considered single-dose nevirapine an optimum regimen; however, the 2004 and 2006 guidelines allowed for single-dose nevirapine in some circumstances (WHO 2004; WHO 2006). By the 2010 revision, single-dose nevirapine was not considered an advisable regimen anywhere (WHO 2010b).

Since 2006, the WHO guidelines have recommended providing ART for pregnant women who require treatment for their own health, and prophylactic ART during pregnancy, childbirth, and at least some period of time after birth for pregnant women who did not satisfy the criteria to begin ART for their own health (WHO 2006). This general approach remains in place through the current 2013 guidelines, although the eligibility criteria for lifelong ART have expanded, and the prophylactic regimen has been strengthened to improve effectiveness, including a recommendation in the 2010 revision to use ART through the entire duration of breastfeeding (WHO 2010b).

There is little evidence on the effectiveness of the exact regimen recommended in the current WHO guidelines, but the findings from studies testing various combination ARV regimens have led to a general consensus that appropriate intervention can reduce MTCT rates to less than 5 percent in breastfeeding populations (Thomas et al. 2011; Tonwe-Gold et al. 2007; SWEN Study Team 2008; Kilewo et al. 2008; Kilewo et al. 2009; Coovadia et al. 2012; Kumwenda et al. 2008; Chasela et al. 2010; Jamieson et al. 2012; Kesho Bora Study Group 2011; Shapiro et al. 2010).

Treatment innovations and increased availability of resources have been associated with a rapid increase in coverage of EMTCT services, and a decrease in the number of HIV infections and HIV-related deaths in infants (UNAIDS 2013). As of 2011, however, many countries were still using EMTCT drug regimens with sub-optimal efficacy, such as single-dose nevirapine (UNAIDS 2011). In 2012, coverage of EMTCT programs using multiple ARV drug regimens was estimated at 62 percent (UNAIDS 2013).

Interpretation of mortality rates among children of HIV-positive women also requires an understanding of the coverage and effectiveness of interventions for children who acquire HIV from their mothers. Estimates for 2012 indicate that only 34 percent of eligible children were receiving ART (UNAIDS 2013). Low coverage of programs for early infant diagnosis of HIV is one of many gaps in the EMTCT cascade contributing to lower coverage of ART and high mortality among children infected with HIV (Wettstein et al. 2012).

2.4. Differential Mortality Rates among Children of Women with and without HIV

Having reviewed the evidence on the rates of MTCT, risks of mortality among children who acquired HIV from their mothers, and the effectiveness and coverage of EMTCT interventions, this report now discusses the findings from the published literature on differential mortality rates among children born to HIV-positive and HIV-negative mothers.

Several prospective studies have been conducted in both clinic-based and population-based cohorts to compare the mortality rates of children born to HIV-positive and HIV-negative mothers. Zaba and colleagues analyzed the data from population-based cohort studies in Malawi, Uganda, and Tanzania in order to calculate excess child mortality due to maternal HIV infection (Zaba et al. 2005). The original studies were conducted in the 1980s and 1990s, when few women had access to EMTCT interventions. Across the three studies, the mortality rates of children of HIV-positive women were almost three times those of children of HIV-negative women. The probability of death by age 1 was 20 percent for children born to HIV-positive mothers, compared with 7 percent for children born to HIV-negative mothers. The probability of death by age 5 was 35 percent for children of HIV-positive mothers versus 11 percent for children of HIV-negative mothers. The analysis also found that the increased risk of mortality for children of HIV-positive mothers compared with children of HIV-negative mothers to be greatest during the first year of life and to decrease steadily with age.

Studies among clinic populations have also found a statistically significant increased risk of mortality among children of HIV-positive mothers compared with children of HIV-negative mothers, in spite of widespread use of single-dose nevirapine and use of ART among some women. Compared with children of HIV-negative mothers, mortality among children of HIV-positive mothers was 2.3 times higher in the first year of life in a study in Mozambique, three times higher by age 9 months in a study in Zimbabwe, and more than four times higher by age 20 months in a study in Malawi (Naniche et al. 2009; Kurewa et al. 2010; Landes et al. 2012). Breaking down the first year of life into the first month (the neonatal period) and the remaining 11 months (the postneonatal period), the study in Mozambique found that all of the increased risk occurred during the postneonatal period, with no statistically significant differences found between the two groups in neonatal mortality (Naniche et al. 2009).

Some studies have also compared the mortality rates of uninfected children born to HIV-positive mothers with those of children of HIV-negative mothers to examine whether or not mother's HIV status may affect their children's likelihood of survival even when the child is HIV-negative. Findings on this subject are mixed, with some analyses finding a significantly increased risk for HIV-negative children of HIV-positive mothers compared with children of HIV-negative mothers (Brahmbhatt et al. 2006; Marinda et al. 2007), and others not (Landes et al. 2012; Spira et al. 1999). Kuhn and colleagues found that the degree of illness in HIV-positive mothers in Zambia was associated with the risk of death and hospitalization of their uninfected children (Kuhn et al. 2005).

The death of the mother has a strong association with child mortality among children of both HIV-positive and HIV-negative mothers (Zaba et al. 2005; Newell et al. 2004a; Dabis et al. 2001; Landes et al. 2012; Brahmbhatt et al. 2006; Kurewa et al. 2010). The analysis of three population-based studies by Zaba and colleagues (2005) perhaps lays out this relationship most clearly. Children of both HIV-positive and HIV-negative mothers experienced a risk of mortality during the time period one year before and two years after the mother's death almost four times as high as children whose mothers did not die during the study period. Overall, 3 percent of children born into the three study populations experienced the death of their mothers: 1 percent of children born to HIV-negative mothers compared with 22 percent of children born to HIV-positive mothers. More recent work suggests that maternal mortality (deaths during pregnancy, childbirth, or in the 42 days following a birth) is eight times higher among HIV-positive women than HIV-negative women (Zaba et al. 2013). Clearly, increased risk of mother's death is one way

maternal HIV status may increase the risk of mortality among both HIV-negative and HIV-positive children of HIV-positive mothers.

2.5. DHS Data in Context: What Do We Expect to Find?

The populations included in this analysis will fall somewhere between the best- and worst-case scenarios outlined in the preceding sections. In the worst-case scenario, MTCT rates are estimated at 25-45 percent, and roughly half of infected children will die before their second birthday. Mortality rates of children under age 5 who are born to HIV-positive women could be three times as high as the mortality rates of children born to HIV-negative women. In the best-case scenario, with the interventions recommended under current WHO guidelines, MTCT is anticipated to decrease to close to 5 percent, and optimal ART coverage for all children and eligible women could largely eliminate the increased risk of mortality for children of HIV-positive mothers.

Given the rapid changes in EMTCT interventions, interpreting the data in this analysis requires an understanding of two important issues of timing: (1) what time period the mortality rates refer to, and (2) when children in this analysis are likely to have been at risk of acquiring HIV, relative to the time of data collection. The year of data collection for the surveys in this analysis ranges from 2003 to 2012. However, the mortality rates measured in each survey represent the risk of death during a period of five years preceding data collection. Furthermore, the year of birth of some children included in the mortality estimates will have occurred before this five-year reference period. For example, a child who has survived to age 4 and whose fourth birthday was at the beginning of the five-year reference period would have been born nine years before the survey. Children are at risk for MTCT during pregnancy, childbirth, and breastfeeding, so the time during which some of the children are likely to have been exposed to infection could extend back nearly a decade before the survey. Children who were born in the decade before the survey, but who died before the start of the five-year reference period are excluded. So the births stretching back eight to nine years will comprise relatively few of the births of children included in the analysis. Further, children with these “very early births” will only be included in those mortality rates that include children who died at older ages (i.e., the child mortality rates and under-five mortality rates, as defined in the Methods section of this report).

Due to these timing issues, the percentage of women and children in these surveys who received any ARV drugs, much less the more effective EMTCT regimens that are currently recommended, is likely to be low. Single-dose nevirapine is likely to have been the national protocol for EMTCT during part of the reference periods for many of these surveys. As summarized above, WHO did not make a strong recommendation for countries to plan to phase out this regimen until 2006, and the WHO guidelines did not recommend ARV use throughout the duration of breastfeeding until 2010. Further, national EMTCT programs cannot adjust to these changes immediately. Countries need time to incorporate new recommendations into their national protocols and to change clinical practice. Fourteen of the twenty surveys in this analysis were completed in 2010 or earlier. In addition to less effective regimens being used in earlier years, the coverage of these regimens was also lower. For example, in 2005, the percentage of pregnant women receiving any ARVs to prevent MTCT, including for their own health, was estimated at only 15 percent in sub-Saharan Africa and 22 percent in the Caribbean. By 2008, coverage is estimated to have expanded to 45 percent in sub-Saharan Africa and 52 percent in the Caribbean (WHO 2010c).

The literature provides some information about what to expect in terms of differences in excess risk of mortality due to maternal HIV by age of the child, but few clinical trials or prospective observational studies followed children long enough to have information on mortality up to age 5. The evidence suggests that differences in mortality between children of HIV-positive and HIV-negative women may be higher in the first year or two of life, with the exception of the neonatal period, where mortality rates have been found to be similar.

There are some reasons to expect that data from DHS surveys may show smaller differences between the mortality rates of children of HIV-positive and HIV-negative women than those in the published literature. DHS surveys differ from other sources of data on maternal HIV and child mortality in that they are cross-sectional. The cross-sectional nature of the data can produce several biases in this analysis (discussed in detail in the Limitations section), most of which would have the effect of underestimating the risk of mortality of children of HIV-positive women relative to the mortality of children of HIV-negative women. In addition, the small numbers of HIV-positive women in surveys for lower prevalence countries result in small numbers of children of HIV-positive women and low statistical power to detect statistically significant differences between the mortality rates of these children and those of children of HIV-negative women.

3. Data and Methods

The study uses data from DHS surveys and AIDS Indicator Surveys (AIS) that included a full birth history to measure childhood mortality, HIV serology testing, with the datasets for both available for analysis, and at least 120 children under age 5 exposed to the risk of mortality in each of the smaller age groups in the 0-4 years preceding the survey, excluding the month of interview.[1] The group of surveys meeting these criteria includes 20 surveys in 13 countries (see Table 1). As shown in Table 1, the national HIV prevalence estimates among women in these surveys range from less than 3 percent in Haiti to more than 30 percent in Swaziland. Direct mortality rates corresponding to the period of time 0-4 years preceding the survey were calculated for all children whose mothers participated in the survey HIV test, and then separately for children of HIV-positive and HIV-negative women.[2] Calculation of the mortality rates followed the standard procedures of the DHS Program, described elsewhere (Rutstein and Rojas 2006). The mortality rates are weighted by the HIV sample weight. The component mortality rates are defined as follows:

Neonatal mortality:	The probability of dying in the first month of life
Postneonatal mortality:	The probability of dying after the first month of life but before the first birthday, calculated by convention as the difference between the infant mortality rate and the neonatal mortality rate
Infant mortality ($_1q_0$):	The probability of dying before the first birthday
Child mortality ($_4q_1$):	The probability of dying between the first and fifth birthdays
Under-five mortality ($_5q_0$):	The probability of dying before the fifth birthday

Mortality rates, standard errors (SE), and confidence intervals were produced using SAS.[3] Unadjusted relative risks, defined as the ratio of the probability of dying among children of HIV-positive women to the probability of dying among children of HIV-negative women, were calculated for the five component rates for each survey in Excel using a two-tailed *t*-test. P-values were calculated in Excel using a normal approximation. A relative risk (RR) of greater than 1.0 indicates a higher risk of mortality for children of HIV-positive women compared with children of HIV-negative women, while an RR of less than 1.0 indicates a lower risk of mortality for children of HIV-positive women.

The mother's HIV status is her HIV status at the time of the survey. HIV status of the mother at the time of the birth is not known, and may differ from her status at the time of the survey. HIV status of children is not known, nor is their exposure to any EMTCT interventions. No information is given on the cause of death.

[1] The smaller age groups are defined as 0, 1-2, 3-5, 6-11, 12-23, 24-35, 36-47, and 48-59 months. Month 0 is used for neonatal mortality, all age groups 0-11 months are used for infant mortality and postneonatal mortality (because postneonatal mortality is calculated as the difference between infant and neonatal mortality), age groups 12-59 months are used for child mortality, and all age groups are used for under-five mortality.

[2] In many of these surveys, HIV testing was conducted in a sub-sample of households. The "total" mortality rates in this analysis may differ slightly from those published in the survey reports due to the exclusion of children whose mothers were not tested for HIV.

[3] The confidence intervals used in this report correspond to ±2SE, and are thus slightly wider than a typical 95 percent confidence interval, slightly increasing the chance of rejecting a true association.

Table 1. Surveys included in the analysis, HIV prevalence, number of women tested for HIV, number of HIV-positive women in the survey, and total fertility rate

Country	Survey name	HIV prevalence among women age 15-49 (weighted)	Number of women tested (unweighted)	Number of women HIV+ (unweighted)	Total fertility rate (TFR)
Sub-Saharan Africa					
Cameroon	Cameroon DHS 2004	6.6	5,155	349	5.0
Cameroon	Cameroon DHS 2011	5.6	7,254	434	5.1
Cote d'Ivoire	Cote d'Ivoire AIS 2005	6.4	4,540	255	4.6
Cote d'Ivoire	Cote d'Ivoire DHS 2011-12	4.6	4,656	209	5.0
Ethiopia	Ethiopia DHS 2011	1.9	15,517	358	4.8
Gabon	Gabon DHS 2012	5.8	5,490	315	4.1
Kenya	Kenya DHS 2003	8.7	3,273	275	4.9
Kenya	Kenya DHS 2008-09	8.0	3,811	318	4.6
Lesotho	Lesotho DHS 2004	26.4	3,034	788	3.5
Lesotho	Lesotho DHS 2009	26.7	3,849	997	3.3
Malawi	Malawi DHS 2004	13.3	2,864	421	6.0
Malawi	Malawi DHS 2010	12.9	7,398	890	5.7
Rwanda	Rwanda DHS 2005	3.6	5,663	222	6.1
Rwanda	Rwanda DHS 2010	3.7	6,952	266	4.6
Swaziland	Swaziland DHS 2006-07	31.1	4,584	1,438	3.8
Tanzania	Tanzania AIS/MIS 2007-08	6.6	8,711	408	5.6
Zambia	Zambia DHS 2007	16.1	5,715	947	6.2
Zimbabwe	Zimbabwe DHS 2005-06	21.1	7,494	1,553	3.8
Zimbabwe	Zimbabwe DHS 2010-11	17.7	7,852	1,463	4.1
Latin America/ Caribbean					
Haiti	Haiti DHS 2012	2.7	9,329	249	3.5

Note: TFR refers to the average number of live births a woman would have if she were subject to the current age-specific fertility rates throughout her reproductive years (age 15-49). Calculated for the three years preceding the survey.

3.1. Limitations

There are many limitations to any analysis on maternal HIV status and child mortality that uses cross-sectional data, as these surveys do. Two of these limitations relate to the potential for underestimating the mortality rates for children of HIV-positive women relative to those of children of HIV-negative women, while two others address the limited nature of the data available.

1. Children of deceased mothers are excluded. As noted above, the literature provides evidence that children of deceased mothers are at increased risk of mortality, and that children of HIV-positive women are more likely to experience a mother's death than children of HIV-negative women. The proportion of children who are excluded due to the death of their mother (and are at higher risk of mortality themselves) will be greater in the group of children of HIV-positive women than

in the group of children of HIV-negative women. Therefore, this selection bias would result in greater underestimation in the mortality rates of children of HIV-positive women than in the mortality rates of children of HIV-negative women, potentially making the mortality rates for these two groups appear to be more similar than they really are.

2. Children are classified by the HIV status of their mothers at the time of the survey, rather than the mother's status at the time of pregnancy, delivery, or breastfeeding. Some women who are currently HIV-positive could have seroconverted since the time they were at risk for passing HIV to their children. Thus, some unexposed children will be included in the 'exposed' group. This misclassification could result in an underestimation of the mortality rates of children of HIV-positive women and thus the degree to which children of HIV-positive women are at increased risk of death compared with children of HIV-negative women.

3. There is no information on the HIV status of children, either surviving or dead. The proportion of children of HIV-positive mothers who acquire HIV infection is unknown. It is not possible to compare MTCT rates across countries or over time, to assess mortality rates of HIV-positive children verses HIV-negative children, or to look for indirect effects of maternal HIV status on HIV-negative children of HIV-positive women.

4. These surveys were not designed for the purpose of comparing the mortality rates of children of HIV-positive and HIV-negative women. The low numbers of HIV-positive women and of children of HIV-positive women lead to low precision in estimated mortality rates of these children. This low precision is particularly limiting when comparing one mortality rate of children of HIV-positive women with another, for example, across different component mortality rates within a single survey, or comparing rates across surveys to look at trends over time.

4. Results

Table 2 presents the mortality rates and confidence intervals for all children, the children of HIV-positive women, and the children of HIV-negative women, for each survey. Figure 1 compares the mortality rates of children of HIV-positive women with those of HIV-negative women. The group of surveys includes a wide range of mortality profiles. The infant mortality rate (IMR) ranges from 36 per thousand live births in the 2012 Gabon DHS to 90 in the 2004-05 Lesotho DHS. Under-five mortality ranges from 62 per thousand live births in the 2012 Gabon DHS to 147 in the 2004 Cameroon DHS.

Table 2. Child mortality rates and confidence intervals for the 0-4 years preceding the survey, by HIV status of the mother at the time of the survey

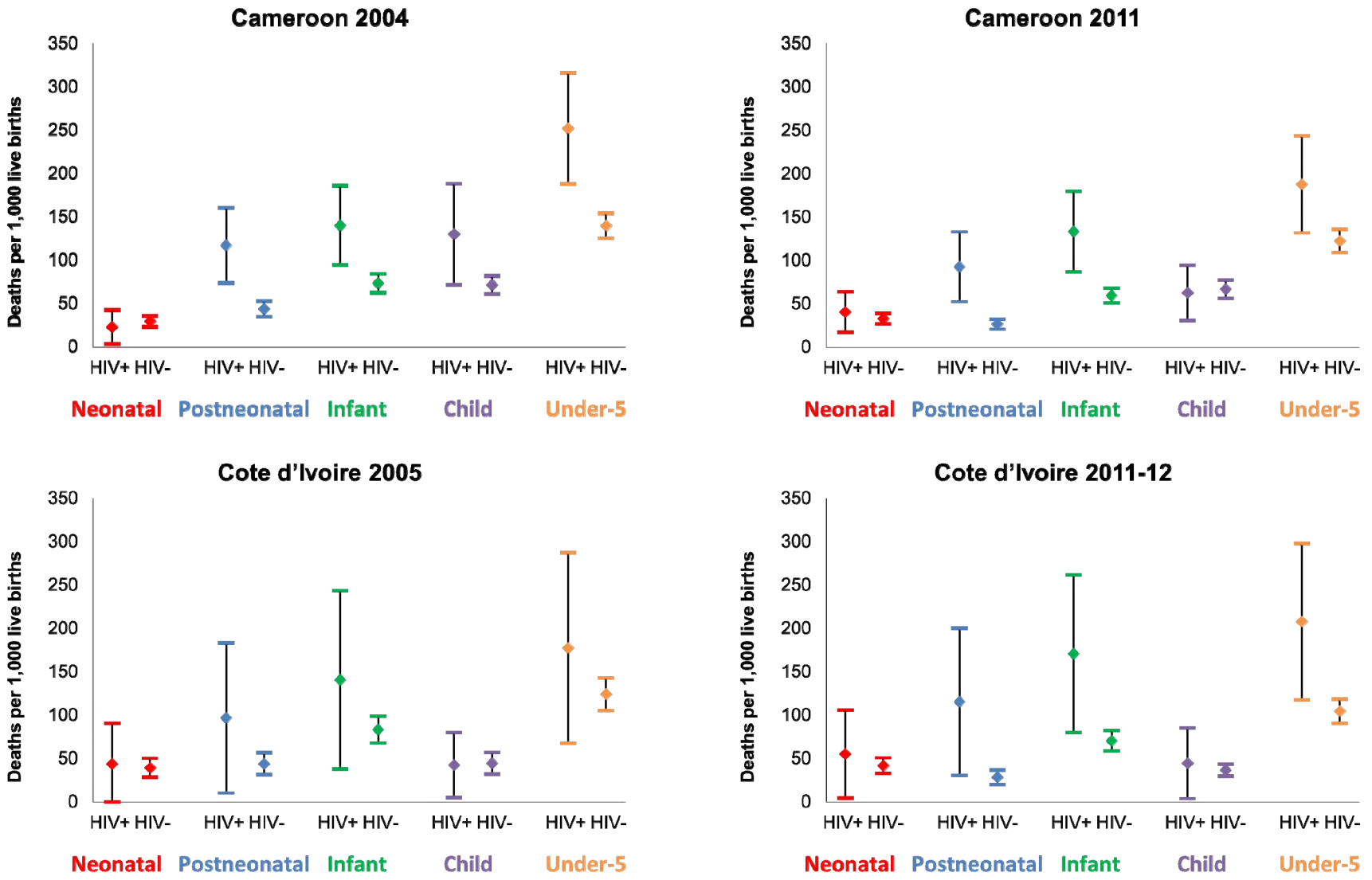
Survey	HIV status of the mother	Neonatal mortality		Postneonatal mortality		Infant mortality		Child mortality		Under-five mortality	
Sub-Saharan Africa											
Cameroon DHS 2004	HIV negative	30	(23, 36)	44	(35, 53)	74	(63, 84)	72	(61, 82)	140	(126, 154)
	HIV positive	23	(3, 43)	117	(74, 161)	140	(94, 186)	130	(72, 189)	252	(188, 316)
	Total	29	(23, 35)	48	(39, 57)	78	(67, 88)	75	(65, 85)	147	(133, 161)
Cameroon DHS 2011	HIV negative	33	(27, 39)	27	(21, 32)	60	(51, 68)	67	(57, 78)	123	(109, 136)
	HIV positive	41	(17, 64)	93	(53, 133)	134	(87, 180)	63	(31, 95)	188	(132, 244)
	Total	33	(27, 39)	30	(24, 36)	63	(55, 72)	67	(57, 77)	126	(113, 139)
Cote d'Ivoire AIS 2005	HIV negative	40	(29, 50)	44	(31, 57)	83	(68, 99)	45	(32, 57)	124	(106, 143)
	HIV positive	44	(0, 91)	97	(10, 184)	141	(38, 244)	43	(5, 80)	178	(68, 288)
	Total	40	(29, 50)	47	(35, 59)	86	(72, 101)	45	(32, 57)	127	(110, 145)
Cote d'Ivoire DHS 2011-12	HIV negative	42	(33, 51)	29	(20, 37)	71	(59, 82)	37	(30, 44)	105	(91, 119)
	HIV positive	55	(5, 106)	116	(31, 200)	171	(80, 262)	45	(4, 86)	208	(118, 298)
	Total	42	(33, 51)	32	(22, 41)	74	(61, 87)	37	(30, 44)	108	(94, 123)
Ethiopia DHS 2011	HIV negative	38	(32, 43)	22	(18, 26)	60	(53, 67)	30	(25, 35)	88	(79, 97)
	HIV positive	49	(0, 105)	16	(0, 38)	65	(5, 125)	49	(8, 90)	111	(42, 180)
	Total	38	(32, 43)	22	(18, 26)	60	(53, 67)	30	(25, 36)	89	(80, 97)
Gabon DHS 2012	HIV negative	23	(16, 30)	14	(9, 19)	36	(28, 45)	28	(19, 37)	63	(51, 76)
	HIV positive	22	(0, 58)	7	(0, 14)	29	(0, 65)	17	(1, 33)	45	(6, 85)
	Total	23	(15, 30)	13	(8, 18)	36	(27, 45)	27	(18, 36)	62	(50, 75)
Kenya DHS 2003	HIV negative	32	(22, 42)	42	(29, 54)	74	(59, 89)	31	(22, 39)	102	(85, 120)
	HIV positive	29	(4, 53)	84	(30, 137)	112	(47, 177)	149	(57, 241)	244	(151, 338)
	Total	32	(23, 41)	46	(33, 58)	78	(62, 93)	42	(30, 54)	117	(97, 136)
Kenya DHS 2008-09	HIV negative	27	(16, 39)	12	(7, 17)	39	(26, 52)	18	(11, 26)	57	(42, 71)
	HIV positive	36	(8, 64)	60	(30, 90)	96	(56, 136)	104	(37, 171)	190	(119, 262)
	Total	28	(17, 38)	16	(10, 21)	43	(31, 56)	25	(16, 34)	67	(52, 83)
Lesotho DHS 2004	HIV negative	42	(27, 58)	27	(17, 38)	70	(52, 87)	22	(11, 32)	90	(70, 109)
	HIV positive	46	(23, 69)	94	(61, 126)	140	(101, 180)	54	(26, 81)	186	(142, 230)
	Total	44	(31, 56)	46	(34, 58)	90	(74, 106)	32	(21, 43)	119	(101, 137)
Lesotho DHS 2009	HIV negative	36	(25, 47)	20	(12, 29)	56	(42, 70)	17	(8, 26)	72	(56, 88)
	HIV positive	47	(18, 76)	102	(72, 132)	149	(106, 192)	57	(32, 81)	197	(153, 241)
	Total	39	(27, 50)	43	(33, 54)	82	(66, 98)	29	(19, 38)	108	(91, 126)

(Continued...)

Table 2. – *Continued*

Survey	HIV status of the mother	Neonatal mortality		Postneonatal mortality		Infant mortality		Child mortality		Under-five mortality	
Malawi DHS 2004	HIV negative	31	(23, 40)	43	(31, 54)	74	(60, 89)	55	(41, 69)	125	(105, 146)
	HIV positive	47	(22, 71)	87	(54, 121)	134	(93, 175)	114	(76, 151)	232	(182, 283)
	Total	33	(25, 41)	48	(37, 58)	81	(67, 94)	62	(49, 75)	138	(119, 157)
Malawi DHS 2010	HIV negative	25	(20, 30)	26	(20, 32)	50	(43, 58)	41	(34, 48)	89	(80, 99)
	HIV positive	41	(22, 61)	78	(52, 103)	119	(88, 150)	108	(76, 139)	214	(176, 252)
	Total	26	(21, 31)	31	(25, 38)	58	(50, 66)	48	(41, 56)	103	(93, 113)
Rwanda DHS 2005	HIV negative	33	(27, 39)	46	(38, 53)	79	(68, 89)	63	(53, 72)	136	(123, 150)
	HIV positive	66	(20, 112)	102	(50, 154)	168	(100, 237)	120	(63, 176)	268	(190, 345)
	Total	34	(28, 40)	48	(40, 56)	82	(71, 92)	65	(56, 74)	141	(128, 155)
Rwanda DHS 2010	HIV negative	32	(26, 38)	25	(20, 29)	57	(49, 64)	25	(20, 30)	80	(72, 89)
	HIV positive	44	(10, 79)	74	(33, 115)	119	(67, 170)	47	(14, 79)	160	(107, 213)
	Total	33	(27, 39)	27	(22, 31)	59	(52, 67)	26	(21, 31)	83	(75, 92)
Swaziland DHS 2006-07	HIV negative	16	(10, 22)	26	(18, 34)	42	(32, 52)	19	(12, 26)	60	(48, 73)
	HIV positive	31	(18, 44)	126	(103, 149)	157	(131, 183)	68	(48, 89)	215	(185, 246)
	Total	22	(16, 28)	65	(55, 76)	87	(75, 100)	38	(29, 47)	122	(107, 137)
Tanzania AIS/MIS 2007-08	HIV negative	28	(22, 33)	28	(23, 33)	56	(48, 63)	33	(27, 39)	87	(78, 95)
	HIV positive	42	(16, 67)	62	(34, 91)	104	(62, 146)	83	(47, 120)	179	(126, 231)
	Total	28	(23, 34)	30	(25, 35)	58	(51, 66)	36	(30, 42)	92	(83, 101)
Zambia DHS 2007	HIV negative	30	(25, 36)	31	(25, 38)	62	(54, 69)	43	(35, 52)	102	(91, 114)
	HIV positive	64	(40, 89)	77	(51, 102)	141	(109, 173)	107	(79, 134)	233	(197, 268)
	Total	35	(29, 41)	37	(31, 44)	72	(64, 80)	52	(45, 60)	121	(110, 131)
Zimbabwe DHS 2005-06	HIV negative	24	(18, 30)	19	(13, 25)	43	(33, 52)	14	(10, 19)	56	(46, 67)
	HIV positive	25	(13, 38)	99	(77, 120)	124	(100, 148)	51	(37, 66)	169	(142, 196)
	Total	24	(19, 30)	37	(30, 44)	62	(52, 71)	23	(18, 29)	84	(73, 95)
Zimbabwe DHS 2010-11	HIV negative	27	(19, 34)	15	(11, 19)	42	(33, 50)	17	(12, 21)	58	(48, 67)
	HIV positive	40	(24, 57)	60	(43, 77)	100	(78, 123)	67	(43, 91)	160	(130, 190)
	Total	29	(22, 36)	23	(18, 27)	52	(44, 59)	26	(20, 32)	76	(67, 86)
Latin America/ Caribbean											
Haiti DHS 2012	HIV negative	33	(26, 40)	25	(20, 31)	58	(50, 67)	29	(23, 36)	86	(75, 97)
	HIV positive	40	(4, 77)	129	(39, 219)	169	(81, 258)	60	(0, 122)	219	(93, 346)
	Total	33	(27, 40)	29	(22, 35)	62	(53, 71)	31	(23, 38)	91	(78, 104)

Figure 1. Childhood mortality ratios by current HIV status of the mother



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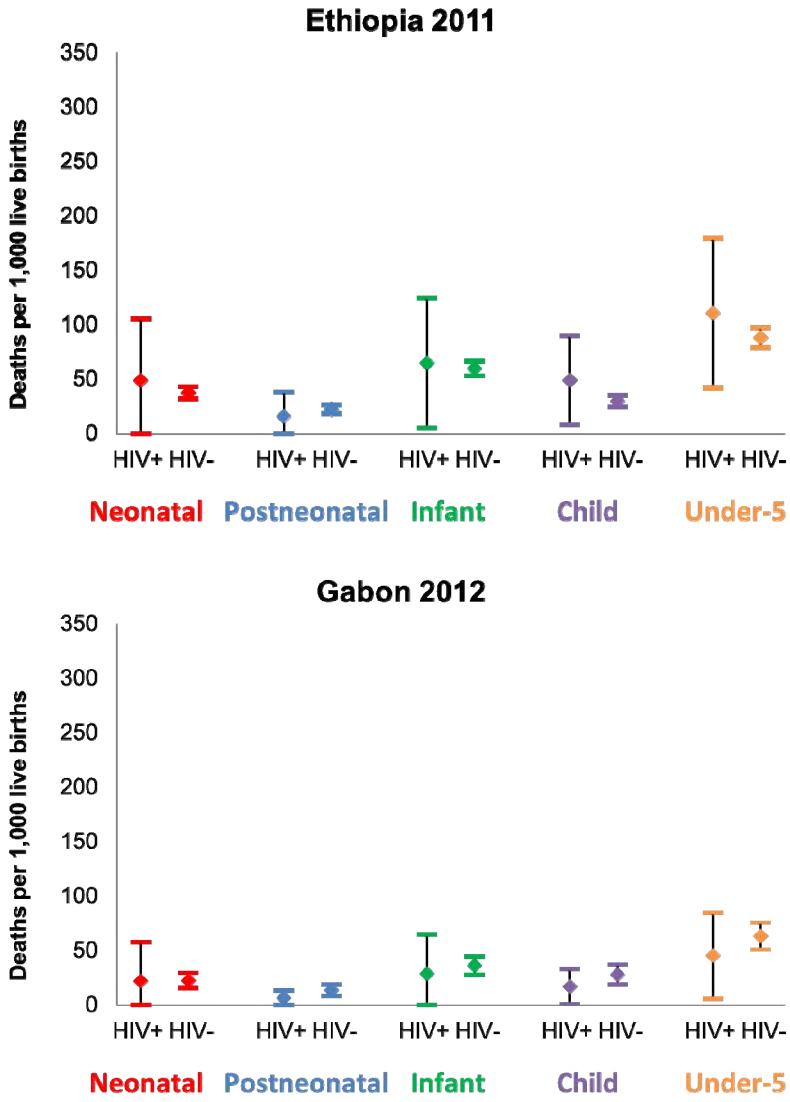

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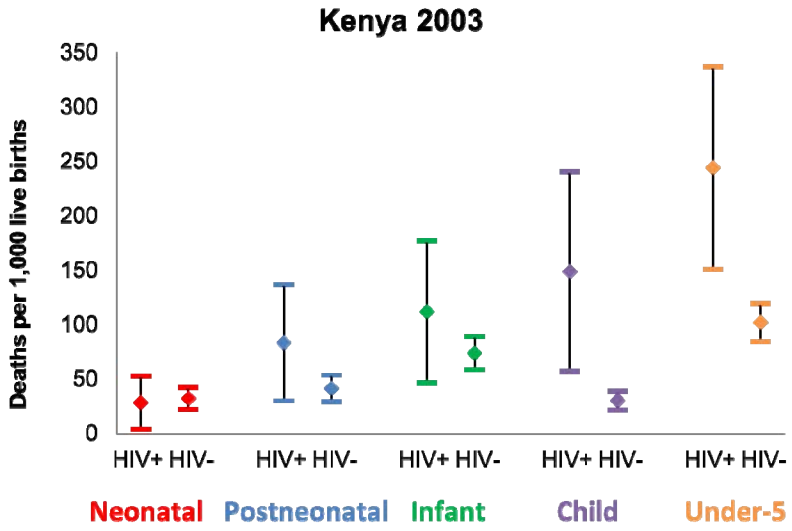

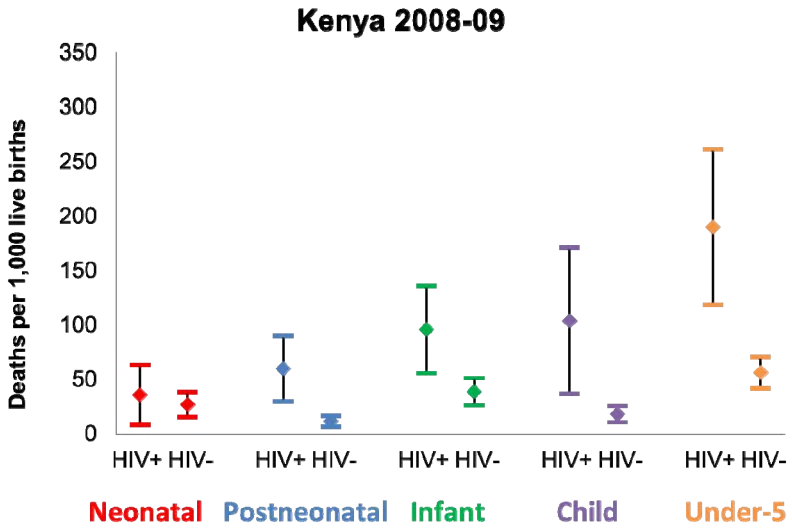

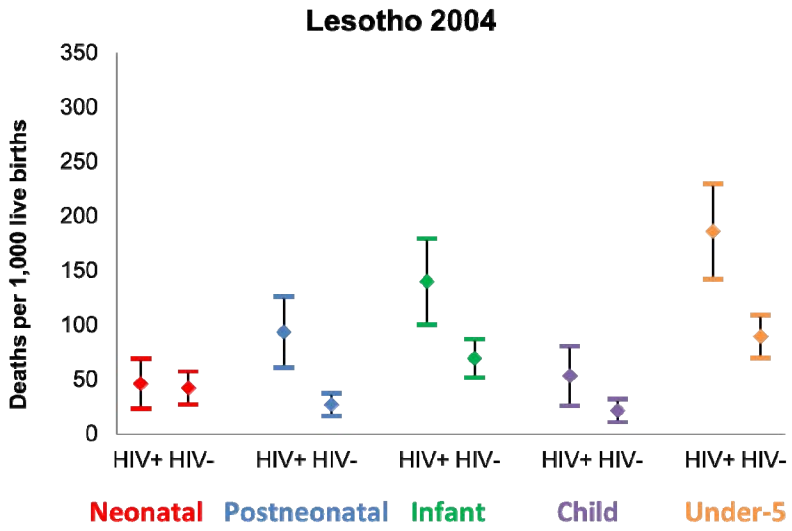

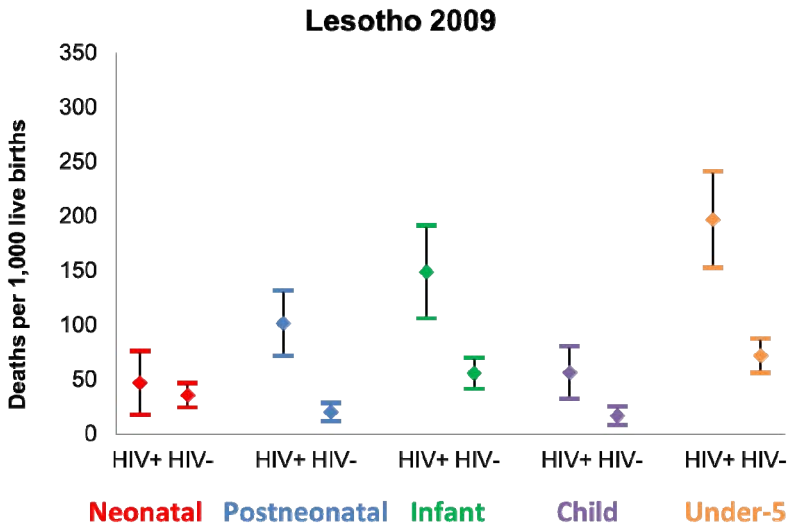

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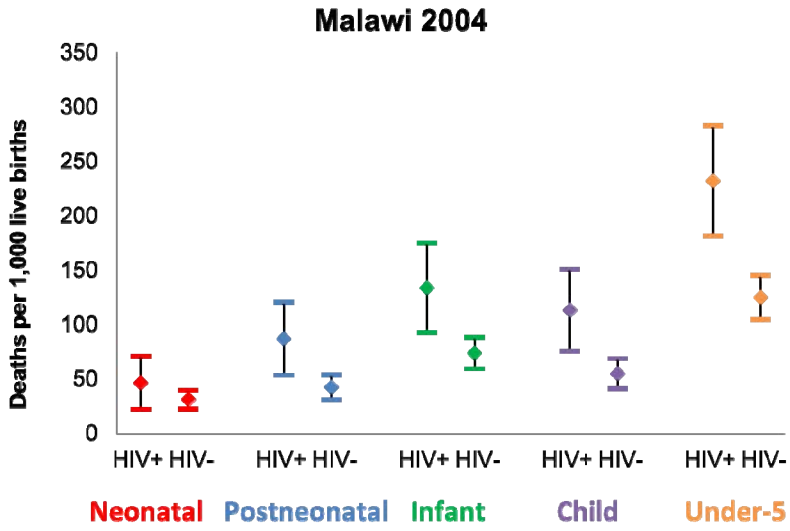

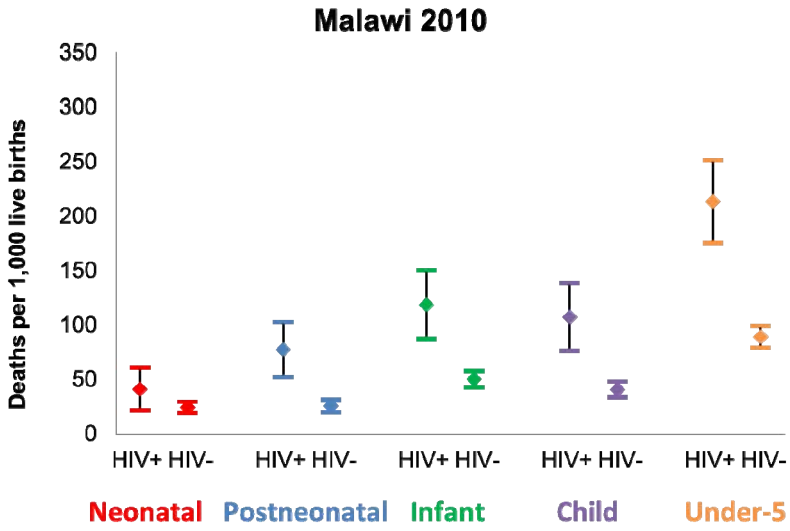

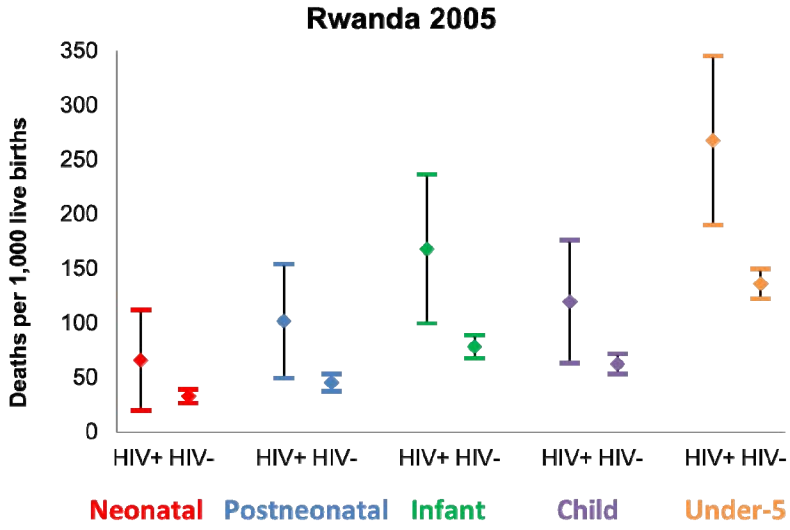

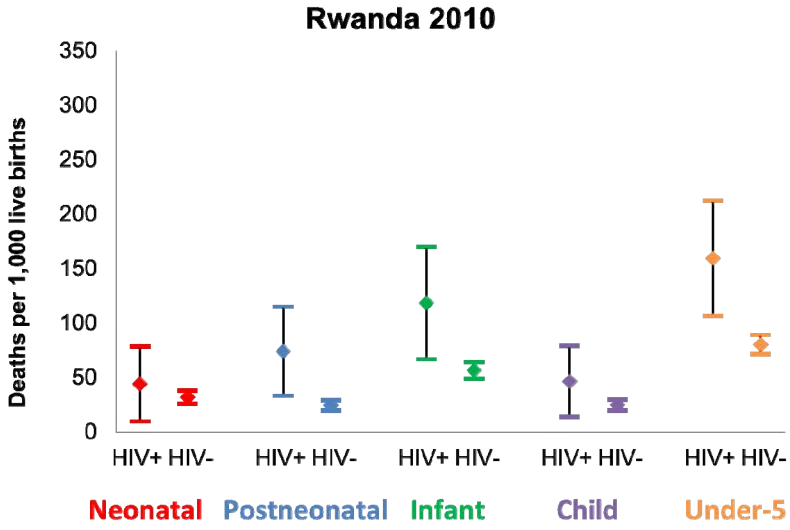

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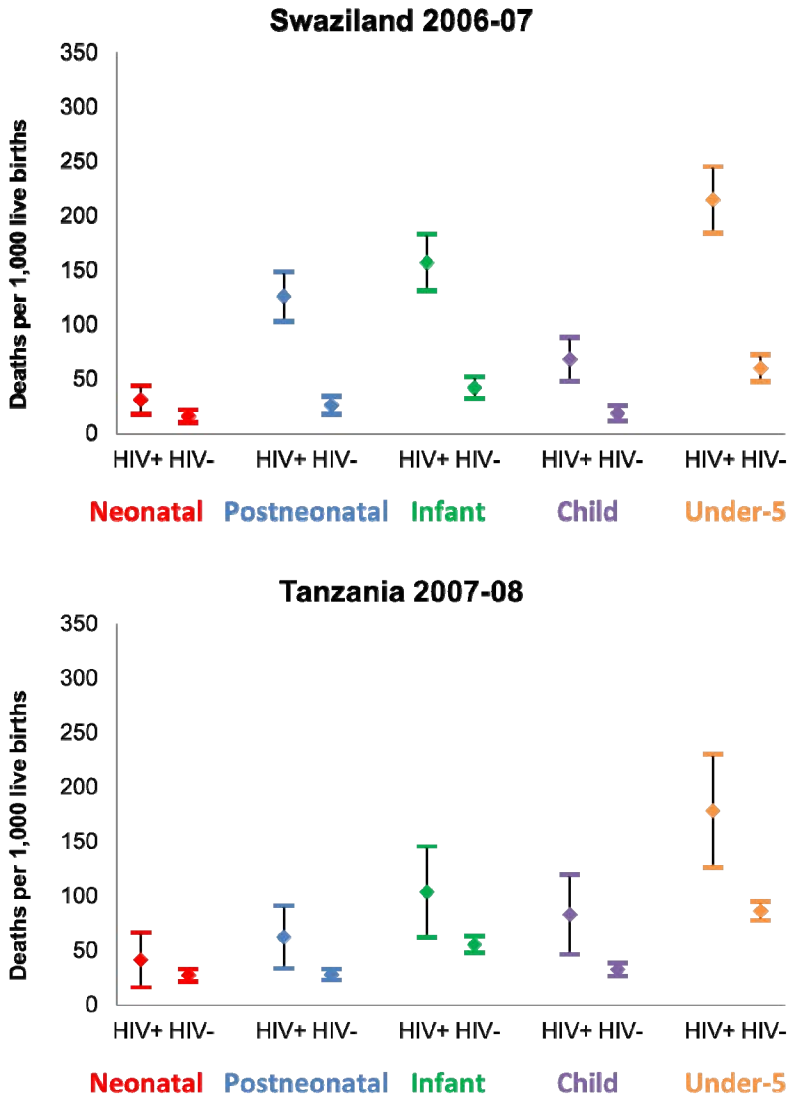

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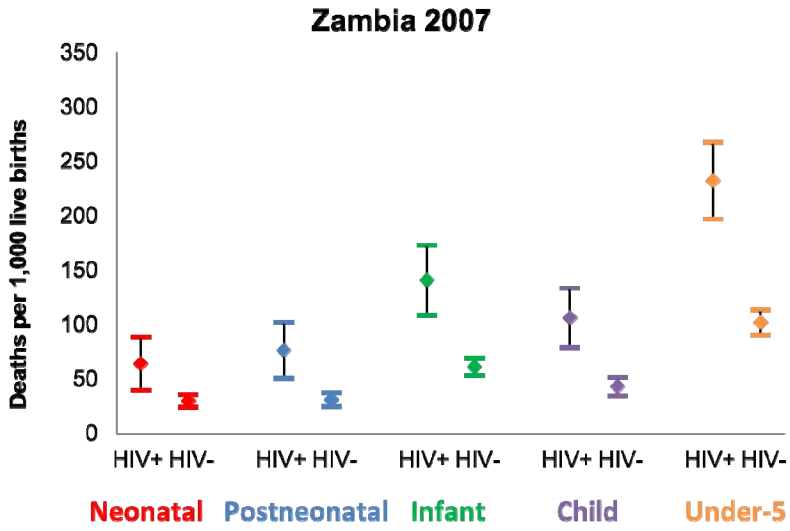

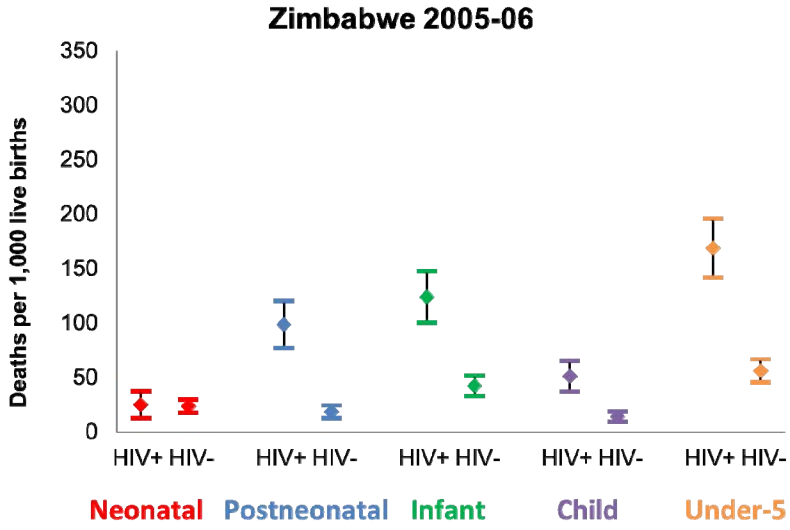

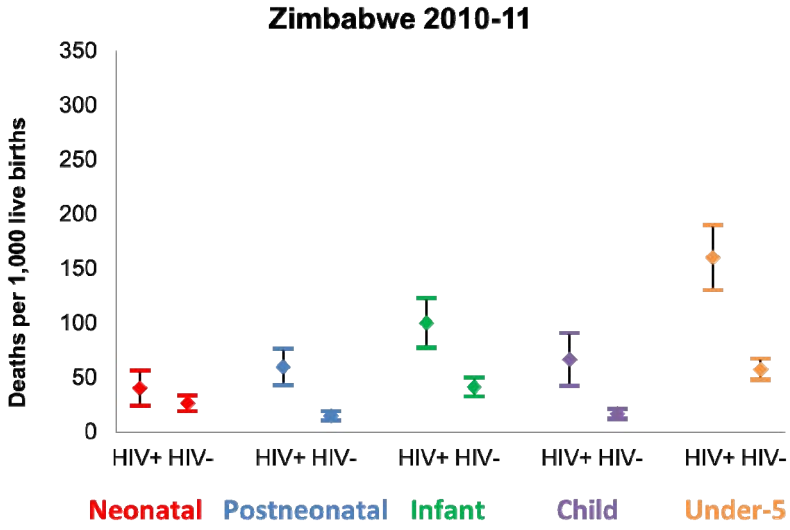

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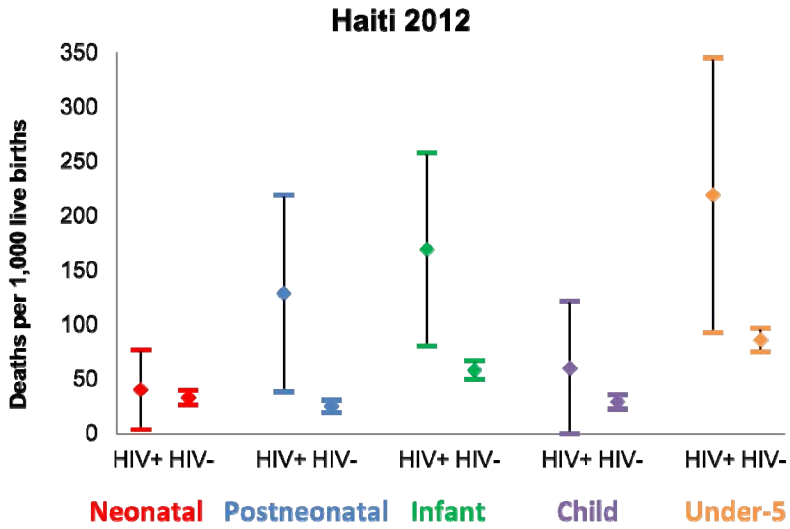


The results demonstrate a higher risk of mortality for children of HIV-positive women. The point estimates for mortality rates for most surveys tend to be higher for children of HIV-positive women than children of HIV-negative women. The confidence intervals for the mortality rates for children of HIV-positive women are much wider than those of HIV-negative women due primarily to the lower numbers of children of HIV-positive women in the survey samples. Despite the low precision of the mortality estimates of children of HIV-positive women, the difference in the mortality rates is large enough in several surveys that the confidence intervals do not overlap.

The wide confidence intervals for children of HIV-positive women also hinder comparisons of their mortality rates at different ages within a survey, but the results show some general patterns. For most surveys, the mortality rates for children of HIV-positive and HIV-negative women are similar during the neonatal period. Evidence of the higher mortality experienced by the children of HIV-positive women begins to appear during the postneonatal period. In most surveys, the neonatal and postneonatal mortality rates tend to be similar for children of HIV-negative women. By contrast, the mortality rates for children of HIV-positive women tend to increase from the neonatal to the postneonatal period (though the increase is within sampling error except in a few higher-HIV prevalence countries).

The IMR includes mortality experienced during the neonatal and postneonatal periods, and is heavily influenced by the neonatal mortality rate because mortality is so high during this period. The IMR may not be the most appropriate rate to use in understanding the impact of mother's HIV status on child mortality because the high levels of background mortality experienced during the neonatal period could dilute the effect of HIV-related mortality occurring later in the first year of life. Nonetheless, the IMRs in the surveys included in this analysis tend to be higher for children of HIV-positive women than those of HIV-negative women.

The child mortality rate does not include the neonatal period, nor the postneonatal period, but it does include a relatively long period of exposure, from age 1 to age 5. If mother's HIV status has a stronger impact on child mortality during the second year of life, for example, than during the third through fifth years, grouping a period of higher risk for HIV-related mortality with a period of lower risk could appear to dilute the effect of mother's HIV status during the younger ages included in the child mortality rate. For the majority of surveys in this analysis, the child mortality rate is lower than the IMR for children of both HIV-positive and HIV-negative women, and child mortality tends to be higher among children of HIV-positive women than among children of HIV-negative women.

Like the IMR, the under-five mortality rate also includes deaths during the neonatal period, although neonatal deaths make up a smaller percentage of the deaths to children under age 5 compared with children under age 1. Deaths during the postneonatal and child periods make up the remainder of deaths in the under-five mortality rate. The under-five mortality rate provides a summary of the overall cumulative probability of death from birth to the fifth birthday. The under-five mortality rates are higher for children of HIV-positive women than those of HIV-negative women for nearly all surveys in this analysis, and the confidence intervals for many surveys do not overlap. The data for the 2012 Gabon DHS do not follow the general pattern. Children of HIV-positive women tend to have lower mortality rates than children of HIV-negative women, though the differences are well within sampling error. The overall mortality rates for this survey are low and may include some underestimation.

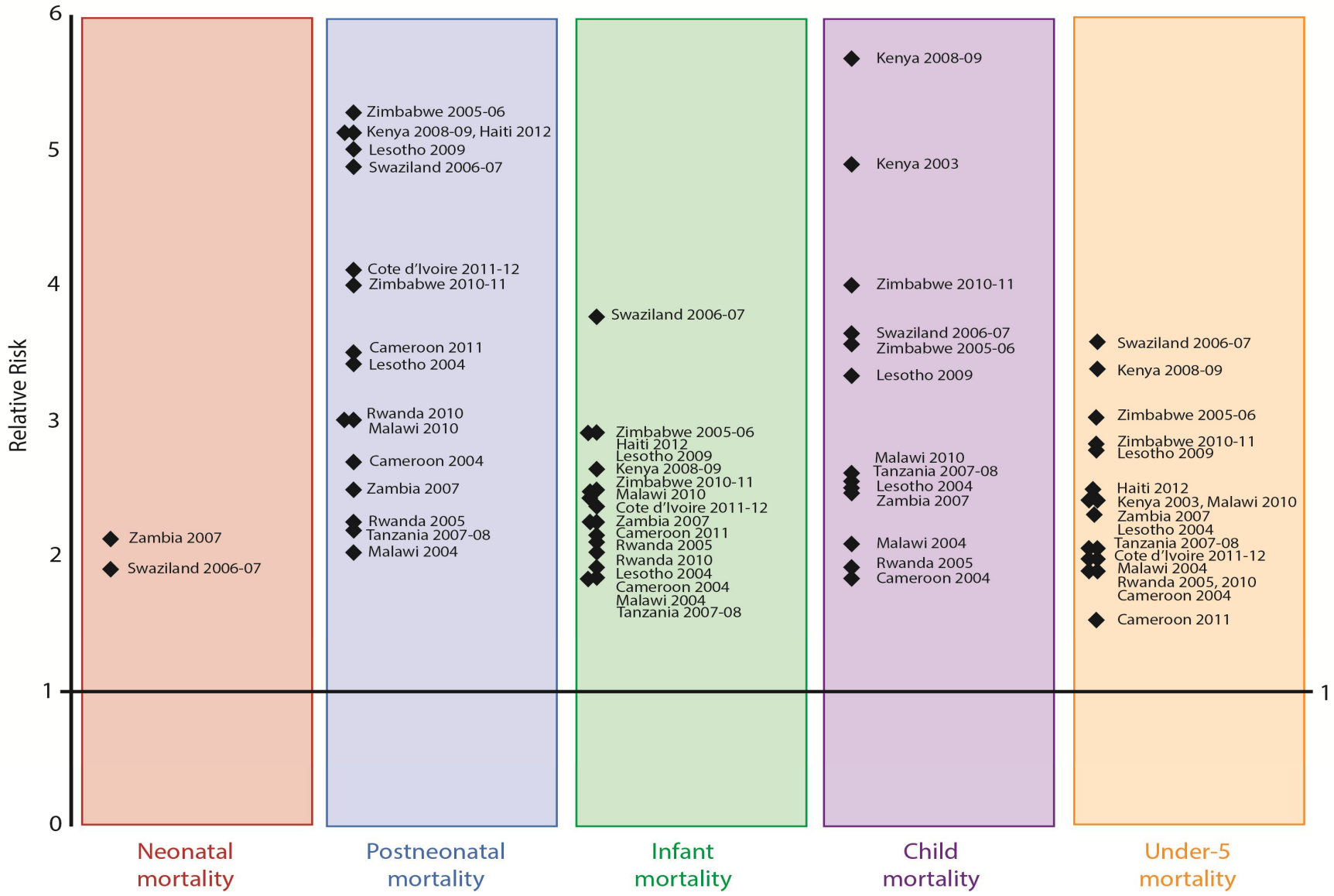
Table 3 shows the unadjusted relative risks (RR) of the mortality of children of HIV-positive women compared with children of HIV-negative women. Figure 2 graphs the relative risks that are statistically significant at a level of $p<0.05$. As seen in Table 3, the vast majority of the relative risks are greater than 1.0, and many are statistically significant, indicating that children of HIV-positive women are at increased risk of mortality compared with children of HIV-negative women.

Table 3. Relative risks of mortality of children of HIV-positive women compared with children of HIV-negative women, 0-4 years preceding the survey

Survey name	Neonatal mortality	Postneonatal mortality	Infant mortality	Child mortality	Under-five mortality
Sub-Saharan Africa					
Cameroon DHS 2004	0.77	2.67 ***	1.90 **	1.82 *	1.80 ***
Cameroon DHS 2011	1.23	3.49 **	2.24 **	0.94	1.53 *
Cote d'Ivoire AIS 2005	1.11	2.20	1.69	0.96	1.43
Cote d'Ivoire DHS 2011-12	1.32	4.03 *	2.42 *	1.21	1.98 *
Ethiopia DHS 2011	1.30	0.71	1.08	1.63	1.26
Gabon DHS 2012	0.98	0.48	0.79	0.61	0.72
Kenya DHS 2003	0.88	2.01	1.52	4.88 *	2.39 **
Kenya DHS 2008-09	1.33	5.10 **	2.47 **	5.67 *	3.36 ***
Lesotho DHS 2004	1.09	3.45 ***	2.02 **	2.48 *	2.08 ***
Lesotho DHS 2009	1.32	5.02 ***	2.66 ***	3.33 **	2.74 ***
Malawi DHS 2004	1.49	2.04 *	1.81 **	2.06 **	1.85 ***
Malawi DHS 2010	1.68	3.00 ***	2.36 ***	2.62 ***	2.39 ***
Rwanda DHS 2005	2.00	2.24 *	2.14 **	1.91 *	1.97 ***
Rwanda DHS 2010	1.38	3.01 *	2.09 *	1.86	1.98 **
Swaziland DHS 2006-07	1.93 *	4.82 ***	3.72 ***	3.65 ***	3.57 ***
Tanzania AIS/MIS 2007-08	1.51	2.22 *	1.87 *	2.54 **	2.06 ***
Zambia DHS 2007	2.13 **	2.45 ***	2.29 ***	2.46 ***	2.27 ***
Zimbabwe DHS 2005-06	1.06	5.26 ***	2.91 ***	3.58 ***	3.00 ***
Zimbabwe DHS 2010-11	1.52	3.99 ***	2.41 ***	3.98 ***	2.78 ***
Latin America/Caribbean					
Haiti DHS 2012	1.22	5.10 *	2.90 *	2.05	2.55 *
Unweighted average relative risk	1.36	3.17	2.16	2.51	2.19

* p<0.05; **p<0.01; ***p<0.001

Figure 2. Relative risk of mortality of children of HIV-positive women compared with children of HIV-negative women, 0-4 years before the survey, only statistically significant results shown



The RRs for neonatal mortality are statistically significant for only a couple of surveys, indicating that the neonatal mortality rates of the children of HIV-positive and HIV-negative women are not significantly different in most surveys. Among the surveys in this analysis, there is little evidence of increased risk of mortality to children of HIV-positive women during the first month of life.

For postneonatal, infant, child, and under-five mortality, the RRs are statistically significant in more than half of the surveys. The statistically significant RRs for postneonatal mortality range from 2.0 in the 2004 Malawi DHS to 5.3 in the 2005-06 Zimbabwe DHS, indicating that children of HIV-positive mothers are two to five times as likely as children of HIV-negative mothers to die between the ages of 1 and 12 months. Most of the statistically significant RRs for infant mortality fall between 2.0 and 3.0, with the exception of the 2006 Swaziland DHS, in which children of HIV-positive women are nearly four times as likely to die before their first birthday compared with children of HIV-negative women. The inclusion of neonatal mortality in the IMR leads to lower relative risks for the IMR than for the postneonatal mortality rate.

For the child mortality rate, most of the statistically significant RRs range from around 2.0 to 4.0, with higher RRs seen for the two Kenya surveys. The statistically significant RRs for under-five mortality range from 1.5 in the 2011 Cameroon DHS to 3.6 in the 2006 Swaziland DHS. The smaller relative standard errors of the under-five mortality rate estimates may contribute to smaller RRs having statistical significance (i.e., being significantly greater than 1.0). The RR of 1.5 for the 2011 Cameroon DHS is the smallest statistically significant RR across all of the component mortality rates. The RRs for under-five mortality are lower than the RRs for postneonatal and child mortality in many surveys, due to the contribution of the neonatal period during which the mortality rates for children of HIV-positive and HIV-negative women are similar.

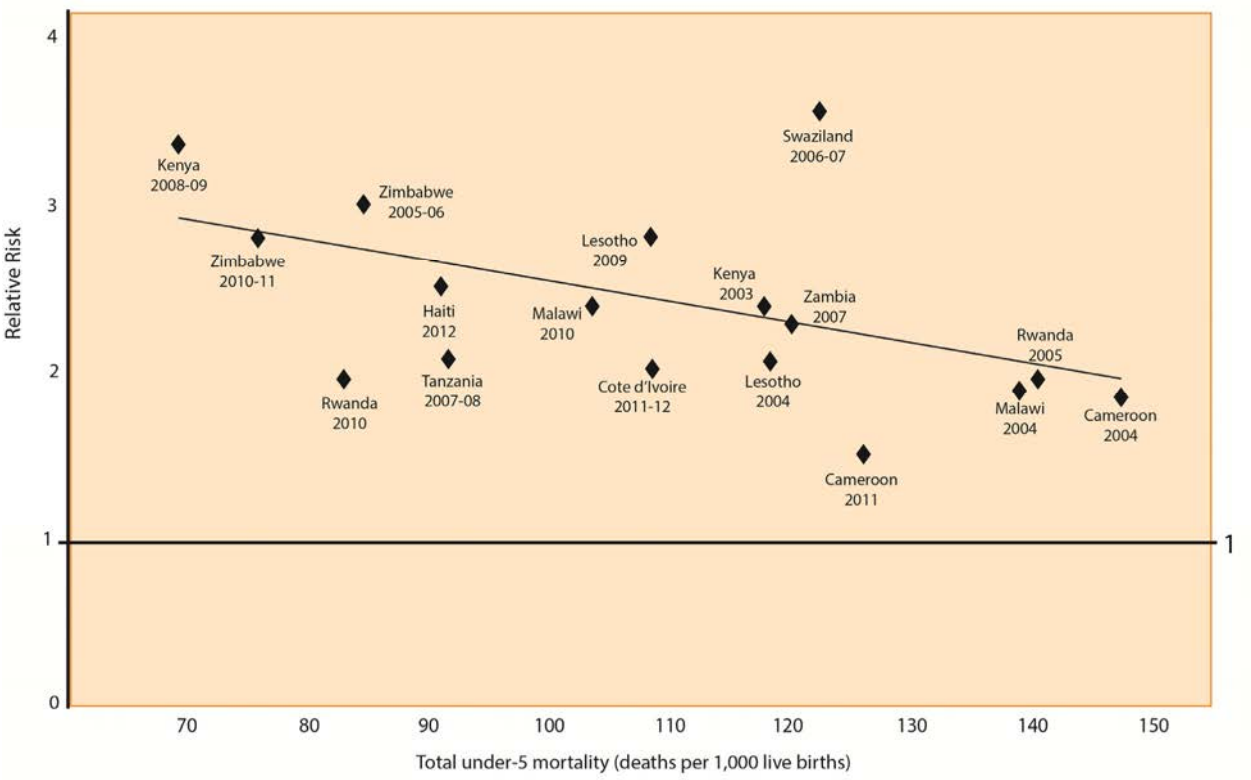
To assess whether or not there are specific ages among children at which maternal HIV infection may be associated with greater increased risk of child mortality, it is necessary to compare the RRs for the neonatal, postneonatal, and child mortality rates. These mortality rates break the first five years of life into three exhaustive and mutually exclusive exposure periods. The mortality rates for the neonatal period show little, if any, increased risk of death for children of HIV-positive women. There is evidence of increased risk for children of HIV-positive women during both the postneonatal and child periods; however, with the variation in the magnitude of the RRs across surveys, it is difficult to compare the risks of mortality during the postneonatal and child exposure periods in this analysis. The postneonatal period includes RRs of 4.0 or higher for the greatest number of surveys, and the simple unweighted average RR across all 20 surveys is 3.2 for postneonatal mortality, compared with 2.5 for child mortality. The highest RRs observed (5.7 and 4.9) are for child mortality, but both figures are from surveys in the same country and are quite a bit higher than the next highest RR of 4.0 for the 2010-2011 Zimbabwe DHS. The findings do not show very strong evidence of decreasing risk of death to children of HIV-positive women compared with children of HIV-negative women during the older ages, as might be suggested by the literature, but the grouping of four years of exposure in the child mortality rate may mask a trend of decreasing relative risk through this period. This hypothesis would be difficult to test with these data, however, given the low number of child deaths between the ages of one and five in individual surveys.

Figure 2 also shows that there is some consistency in the magnitude of the RRs across the different component rates by country. On the one hand, from postneonatal through under-five mortality, Kenya, Swaziland, and Zimbabwe tend to be among the countries with higher RRs for mortality for children of HIV-positive women versus children of HIV-negative women. On the other hand, Cameroon, Malawi, Rwanda, and Tanzania tend to be among the countries with lower RRs.

In theory, when overall levels of child mortality are higher, the proportion of mortality associated with maternal HIV status should be lower, leading to lower relative risks. Figure 3 plots the RRs for the under-

five mortality of children of HIV-positive women compared with children of HIV-negative women against the overall under-five mortality rate for surveys with a RR for under-five mortality which is statistically significant at $p<0.05$. The findings show that, as expected, the under-five RRs tend to decrease as background mortality increases. The RR for the 2006 Swaziland DHS is higher than expected compared with other countries with similar under-five mortality rates.

Figure 3. Relative risk of under-five mortality of children of HIV-positive women to mortality of children of HIV-negative women by survey year, 0-4 years before the survey, only statistically significant results shown



Caution must be used in interpreting trends over time in the mortality of children of HIV-positive women using data from DHS and AIS surveys. First, these surveys do not include information on whether or not a death is HIV-related, so changes in mortality rates to children of HIV-positive women must be interpreted with respect to changes in background levels of mortality. A decrease in mortality to children of HIV-positive women is undoubtedly a positive outcome; however, this cannot necessarily be interpreted as an improvement in the mortality of children of HIV-positive women relative to that of children of HIV-negative children. Similarly, a reduction in the relative risk of mortality for children of HIV-positive women compared with children of HIV-negative women could potentially hide a lack of change, or even an absolute increase in mortality for children of HIV-positive women, if overall mortality for children increased over time.

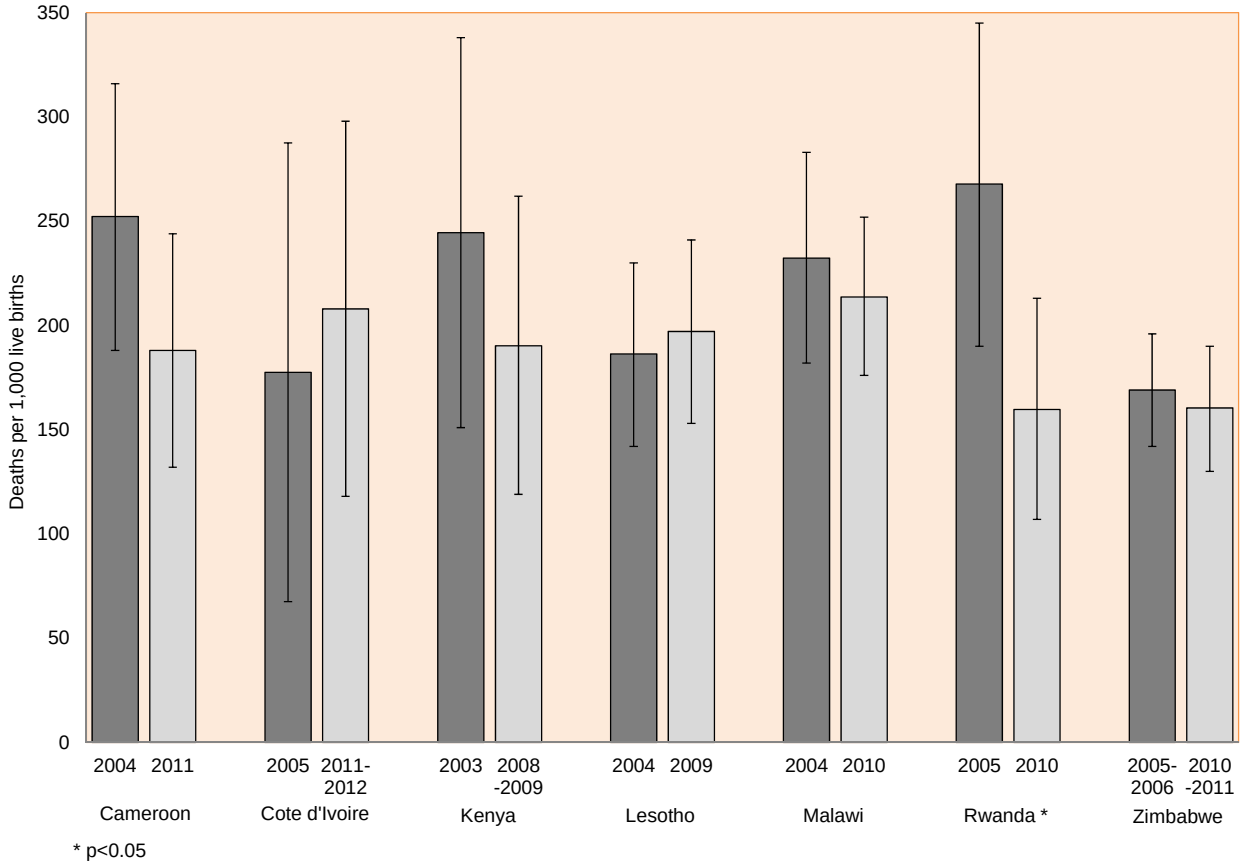
Second, the low precision of the mortality rates for children of HIV-positive women in this analysis results in poor statistical power to assess changes between two surveys. It is possible to make meaningful comparisons between the mortality of children of HIV-positive and HIV-negative children within the

same survey largely due to the fact that the confidence intervals around the mortality rates of children of HIV-negative women are small. Once we begin to compare one mortality rate for children of HIV-positive women with another in this analysis, the large confidence intervals around both rates usually prevent the formulation of any statistically significant findings.

Third, when using the under-five mortality rates for comparison, there could be some overlap in the two survey populations in terms of the time during which children in each survey would have been exposed to the risk of acquiring HIV. Although the pairs of surveys in each country occurred at least five years apart, and there is no overlap in the reference period for exposure to death, some of the births for the later survey could have occurred prior to that survey's five-year reference period and extended back into the reference period for the earlier survey. Finally, it is important to recognize that the reference periods for these surveys are not that recent, especially given the timing of advances in EMTCT programs. A rough average of the mid-points of the reference periods is 2002 for the earlier surveys and 2008 for the later surveys.

Figure 4 shows the under-five mortality rates for the children of HIV-positive women for the seven countries with data available for two surveys. Vertical lines in the Figure show the confidence intervals. There are no consistent findings regarding change in mortality rates of children of HIV-positive women over time. For a few surveys, the under-five mortality rates are roughly the same in the first and second surveys. The rates appear to increase over time in Cote d'Ivoire, but the changes are not statistically significant. Rates appear to have decreased in Cameroon, Kenya, and Rwanda, but among these countries only the change in Rwanda is statistically significant ($p<0.05$). It is important to note, however, that the absolute decrease in mortality of children of HIV-positive women in Rwanda does not represent an improvement in the outcomes of children of HIV-positive mothers relative to those of HIV-negative mothers. In both surveys, children of HIV-positive women were roughly twice as likely as children of HIV-negative women to die before age 5 (see Table 3). It appears that much of the decrease in mortality of children of HIV-positive women can be attributed to the large decrease in under-five mortality for all children in Rwanda over this period (see Table 2).

Figure 4. Trends in under-five mortality rates for children of HIV-positive women, 0-4 years before the survey



5. Conclusions

To our knowledge, this analysis is the first to assess the relationship between maternal HIV status and child mortality using nationally representative data, and the findings largely support the results of the existing body of literature based on cohort studies and clinical trials. The general pattern across these surveys is that children of HIV-positive women experience higher mortality than children of HIV-negative women. In 17 of 20 countries studied, children of HIV-positive women have significantly higher under-five mortality rates than children of HIV-negative women. The increased risk is strong enough to be statistically significant even in surveys with low numbers of children of HIV-positive women. Given the potential for underestimating the mortality of children of HIV-positive women relative to that of children of HIV-negative women (as described in the Limitations section), and the low sample size of children of HIV-positive women, it is notable that the association between child mortality and mother's HIV status is in the expected direction and is statistically significant across so many surveys.

Strictly speaking, this bivariate analysis does not establish whether or not the higher risk of mortality among children of HIV-positive women compared with children of HIV-negative women can be attributed to maternal HIV status, either directly or indirectly. Nevertheless, supporting literature does provide evidence of a causal relationship between maternal HIV-status and child mortality. We do not address here the proximate causes of death.

The analysis of mortality rates for different ages shows that the association between maternal HIV status and child mortality is weakest during the neonatal period. This finding is consistent with studies in the published literature, which tend to find similar mortality rates for children of HIV-positive and HIV-negative women during the neonatal period. The lack of evidence of higher risk of neonatal mortality among children of HIV-positive women may be due to several factors. First, background mortality rates are high during the first month of life. Neonatal deaths account for around one-third of all under-five deaths in the group of surveys included in this analysis. This is consistent with the international estimate of neonatal deaths comprising about one-third (34 percent) of under-five deaths across sub-Saharan Africa (UNICEF et al. 2013). Thus, the relative contribution of HIV-related mortality is likely to be lower during the neonatal period than at older ages. Second, in the absence of intervention, around 40 percent of children who acquire HIV through MTCT become infected with HIV during breastfeeding, and many of these children will become infected after the first month of life. Finally, even for children infected during pregnancy or childbirth, natural-history studies suggest that the excess risk of mortality accumulates gradually over several months.

Statistically significant RRs indicating increased risk of mortality to children of HIV-positive women are found in 17 of 20 surveys for postneonatal mortality, and in 13 of 20 surveys for child mortality. The wide range in the statistically significant RRs during the postneonatal (2.0 to 5.3) and child (1.8 to 5.7) periods makes it difficult to determine which time period may include the greater excess risk of death for children of HIV-positive women; however, the unweighted average RR across the 20 surveys is higher for postneonatal than child mortality (3.2 compared with 2.5). Evidence indicates that the mortality risk for children of HIV-positive women relative to those of HIV-negative women may be greater in the second year of life than at older ages. The long exposure period in the child mortality rate may mask differences in relative risks of mortality within the age range. This topic merits further investigation, perhaps using pooled data since the number of deaths during this age range in individual surveys is low.

There are many limitations in attempting to use these data to evaluate the effectiveness of EMTCT programs. As explained above, MTCT rates cannot be measured—the HIV status of the child and of the mother at the time of the birth are not known. Nor do the surveys collect information on exposure of individual women and children to prevention and treatment interventions. The data available in these

surveys can assess only whether or not there is a broad, population-level association between national advances in EMTCT and child outcomes. However, understanding the population-level coverage of interventions in effect for a survey is also difficult, given the rapid expansion of EMTCT programs that could have occurred within the five-year reference period preceding the survey.

The comparison of successive surveys within each of seven countries in this analysis shows no clear evidence of significant improvement over time in the outcomes of children of HIV-positive women compared with children of HIV-negative women at the population level. Several factors could contribute to this finding. The statistical power could be insufficient to detect a change, or the overlap in the period of exposure to infection for the two surveys could dilute the comparison. Finally, despite remarkable progress in EMTCT programs during and since the time period examined in this analysis, gaps still remain. The coverage and effectiveness of EMTCT programs in place during the reference periods for the later surveys could have been insufficient to have resulted in an improvement in mortality at the population level. For the seven countries with two surveys in this analysis, the mid-points of the five-year reference periods are 2002 for the earlier surveys and 2008 for the later surveys. Given that the WHO guidelines did not completely move beyond single-dose nevirapine or extend the recommendation for use of ART through the duration of breastfeeding until 2010, it is unlikely that many of the children even in the later group of surveys were exposed to the more effective EMTCT regimens currently recommended. The size of the RRs for infant and under-five mortality for children of HIV-positive women versus children of HIV-negative women in this analysis (a two- to three-fold increase) is similar to that observed in clinical trials and cohort studies in populations with minimal exposure to EMTCT programs, or exposure to sub-optimal regimens.

Current international goals call for reducing the number of new HIV infections in children by 90 percent between 2009 and 2015 and reducing the number of AIDS-related maternal deaths by half (UNAIDS 2011). If these goals are achieved, we anticipate that the impact on mortality would be great enough to be observed in future DHS and AIS surveys. The relative risks for the mortality of children of HIV-positive women compared with children of HIV-negative women would decrease over time closer to 1.0 and would lose statistical significance. Due to the five-year exposure period preceding each survey, and the inclusion of births occurring before the start of the exposure period, these achievements would need to be sustained for several years before they could be fully reflected in cross-sectional surveys.

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