

# **A Spreadsheet Model to Estimate the Effects of Different Infant Feeding Strategies on Mother-to-Child Transmission of HIV and on Overall Infant Mortality<sup>1</sup>**

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**January, 1999**

## **ABSTRACT**

**The risk of mother-to-child transmission of HIV during breastfeeding is about 1 in 7. However, under conditions of poverty and poor hygiene, there are few alternatives. The use of breastmilk substitutes may not be affordable or safe and may result in an even higher risk of death due to malnutrition and infection. There is a need for policy makers and health workers to understand how these risks compare in different situations. The spreadsheet described in this document is a risk analysis decision tree. It permits users to conduct simulations of the risk of mother-to-child transmission vs. the risk of death due to artificial feeding in populations affected by HIV. Infant survival is predicted on the basis of the mother's HIV status at delivery, the infant's HIV status at delivery, and the feeding strategy chosen. Virtually any scenario can be simulated for the purposes of policy analysis. For this analysis 17% of infants not infected prior to delivery but breastfed by their HIV infected mothers are assumed to become infected through breastfeeding. In a community where the baseline infant mortality rate (IMR) is 100/1000 live births and where non-breastfed infants are 3 times more likely to die than breastfed infants, the risk of death due to artificial feeding would be greater than the risk of HIV infection through breastfeeding. Artificial feeding would be safer only if the risk of transmission were greater than 22%, the IMR were less than 78/1000 or the relative risk were lower than 2.5. When the mother's status is not known and she is living under conditions of poverty and poor hygiene, breastfeeding is virtually always favored. The analysis presented here considers risk over the entire year of infancy. If risk analysis were to focus only on early infancy, when both infant mortality and the risk of death due to artificial feeding are greatest, breastfeeding would be even more strongly favored.**

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<sup>1</sup> This paper is a product of the LINKAGES (Breastfeeding, Complementary Feeding, and Maternal Nutrition) Project. LINKAGES is supported by the Global Bureau (G/PHN/HN), U.S. Agency for International Development, under Cooperative Agreement no. HRN-A-00-97-00007-00. LINKAGES is managed by the Academy for Educational Development. The opinions expressed herein are those of the author and do not necessarily reflect the views of the U.S. Agency for International Development.

## Introduction

Each year an estimated 600,000 children are infected by HIV, mainly due to transmission from mother to child in the womb, during delivery or through breastfeeding. Most of these infections could be avoided through use of antiretroviral drugs taken during pregnancy and delivery, and avoidance of breastfeeding. Unfortunately, despite the development of shorter antiretroviral regimens and the negotiation of lower drug prices, in most countries with the highest prevalence of HIV, neither government health systems nor families can afford antiretroviral drugs on the scale needed. Ensuring adherence to difficult regimens, maintaining supplies and monitoring and dealing with side effects present logistical difficulties to weak health service delivery systems. Infant formula, the preferred alternative to breastmilk for HIV-positive mothers, is even more expensive and more difficult to administer safely. In any case, these preventive strategies rely on mothers knowing that they are infected but only a tiny proportion of HIV-infected pregnant women know their status. It is therefore important that testing becomes more widely available and accepted, and that effective strategies to prevent mother-to-child transmission (MTCT) of HIV are provided.

However, breastmilk substitutes carry their own risks that need to be balanced against the risk of HIV transmission. As a complete source of the infant's fluid and nutritional requirements, breastmilk is unparalleled. It is usually free of infectious pathogens and contains anti-infective components that protect the infant from diseases that are often fatal, especially in situations where HIV is most prevalent. Breastfeeding also contributes to child spacing, thus benefiting the mother's health and the economy of the entire household. The role of breastfeeding in MTCT therefore presents a serious public health policy dilemma for two reasons.

First, under some circumstances the risk of death due to not breastfeeding may exceed the risk of transmission through breastfeeding. The balance of risks under different conditions is not at all obvious and needs to be examined in each situation. For the mother who knows she is infected and for the healthworker advising her, there is a need to understand the risks of different infant feeding strategies.

Secondly, the promotion and protection of breastfeeding among uninfected mothers is one of the most effective ways to preserve child health and survival, especially under conditions of poverty and poor hygiene, where its nutritional and immunological benefits are most needed. There is concern that the promotion and use of breastmilk substitutes among HIV+ mothers will "spill over" into the uninfected population. If testing is not universally available, uninfected mothers who suspect that they are infected may inappropriately modify their infant feeding strategy by replacing or supplementing breastmilk with substitutes.

Current international policy recommendations (UNAIDS/WHO/UNICEF, 1997) call for women to "be empowered to make fully informed decisions about infant feeding" but until the risks associated with different infant feeding decisions are better understood it is difficult to imagine how women can be "fully informed." UNAIDS recently announced pilot studies that will provide a package of services to reduce MTCT, including AZT and infant formula (UNAIDS, 1998). This initiative makes the need to understand the overall mortality risks associated with different infant feeding strategies under different conditions even more pressing. The spreadsheet model described here allows policy analysts to simulate the impact of such programs.

A number of studies have been published that use similar simulation tools to answer similar questions (Heymann, 1990; Hu et al., 1992; Kennedy et al., 1990, 1992; Del Fante et al., 1993; Nagelkerke et al., 1995; Kuhn and Stein, 1997). These have been summarized recently by Preble and Piwoz (1998). The purpose of this paper and the spreadsheet it describes is to make this tool more widely available to analysts interested in conducting their own simulations. They can request a copy of the spreadsheet from the author or use the formulae provided here to construct their own software tools.

In this paper, assuming a set of conditions that prevail in many situations where HIV prevalence is high, the following questions are addressed using this model:

- What is the predicted impact on infant mortality of a substantial shift toward breastmilk substitutes among HIV-infected mothers?
- What is the predicted impact on infant mortality if there is also a shift toward breastmilk substitutes among uninfected mothers?
- What are the predicted impacts on infant mortality of different infant feeding strategies in situations where the status of mothers is not known?
- How sensitive are answers to these questions to the values of key variables that may be uncertain or subject to policy influence (such as the underlying infant mortality rate, the relative risk of death due to artificial feeding, or the rate of transmission through breastfeeding)?

## **Methods**

### ***Model structure and design***

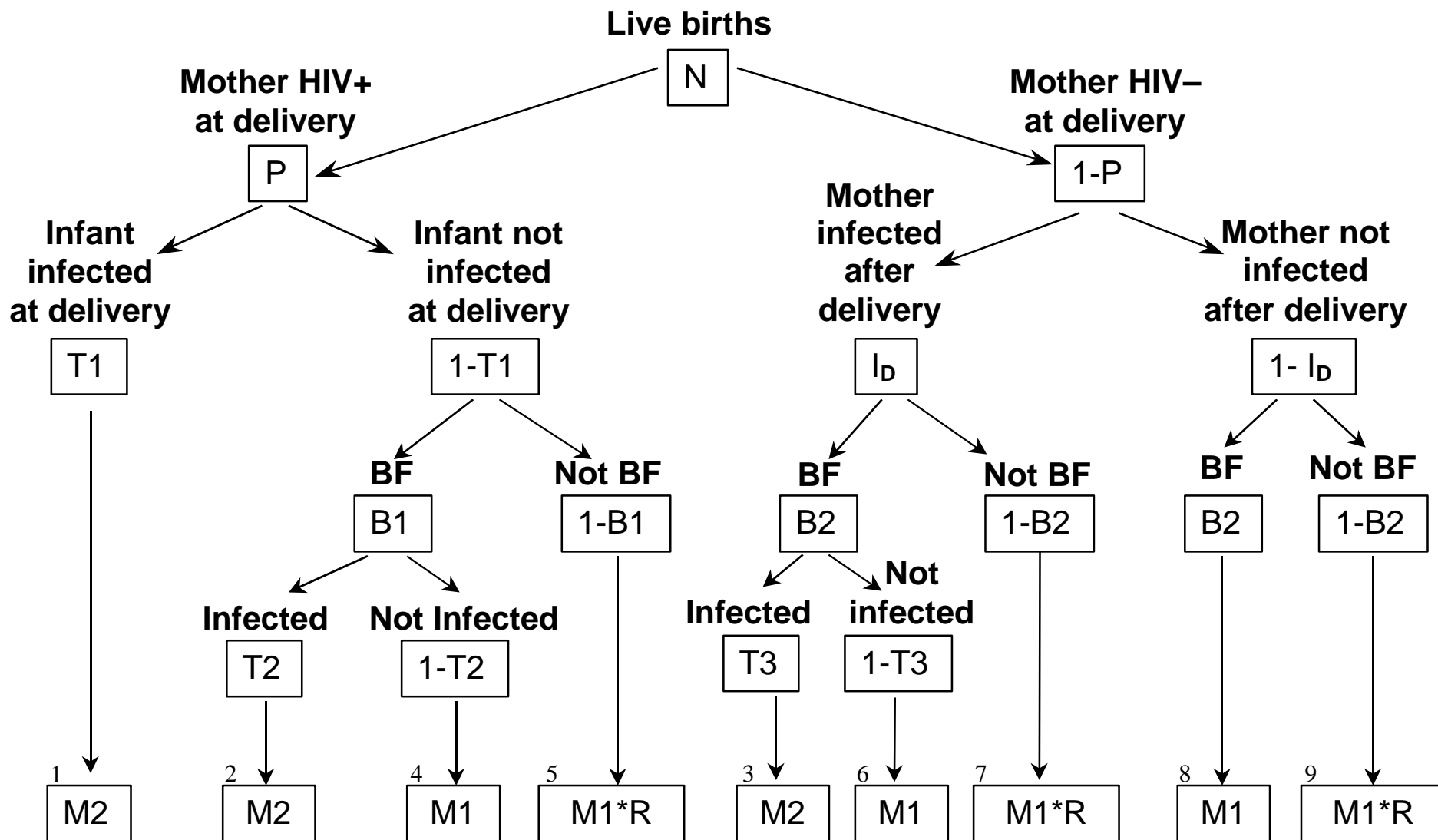
The spreadsheet is designed to simulate one scenario or set of conditions at a time. Each set of conditions is captured by the values of 12 variables listed in Table 1. Total infant mortality for each scenario is estimated by calculating the mortality risk in each of 9 mutually exclusive categories, as illustrated in the accompanying “decision tree” (Figure 1) and described in Table 2. This model is based on one originally presented by Hu et al. (1992). The spreadsheet is distributed with a set of values representing a baseline scenario that can be changed by the user to reflect any other scenario of interest.

### ***Technical Assumptions***

The baseline value for the number of live births (N) is 1000, simply because this is the denominator of the infant mortality rate. Estimates for the prevalence of HIV among pregnant women (P) are generally available. The incidence of new infections among mothers after delivery (I) is used in the model to estimate the number of deaths due to transmission through breastfeeding by a newly infected mother. When HIV prevalence is stable, a reasonable approximation of I can be obtained by dividing prevalence by average duration from infection to death. (However, this may overestimate the actual postpartum incidence if breastfeeding mothers are less sexually active than the general population.) The duration of breastfeeding (D) is used only to calculate the actual exposure of breastfed infants of mothers infected after delivery and has a baseline value here of 1 (the whole of infancy). The incidence of infection during the

breastfeeding period ( $I_D$ ) is a function of the annual incidence of infection ( $I$ ) and the duration of breastfeeding in years ( $D$ ) and is equal to  $1-(1-I)^D$ , so when  $D=1$ ,  $I_D=I$ .

**Figure 1.** Decision tree showing 9 mutually exclusive categories of infants. The formula for mortality in any category is obtained by multiplying together the cells in that path of the tree (mortality in category 1 is  $N \cdot P \cdot T1 \cdot M2$ , in category 2 is  $N \cdot P \cdot (1-T1) \cdot B1 \cdot T2 \cdot M2$ , etc.). For symbol definitions see Table 1.



**Table 1.** Variable definitions, symbols and baseline values used in risk analysis model.

| <b>Definition</b>  | <b>Symbol</b> | <b>Baseline Value</b> |
|--|---------------|-----------------------|
| Number of live births  | N             | 1000                  |
| HIV Prevalence among childbearing women                        | P             | 0.2                   |
| Annual incidence of new infections among breastfeeding mothers | I             | 0.03                  |
| MTCT rate before and during delivery                           | T1            | 0.2                   |
| MTCT rate during breastfeeding (HIV+ at delivery)              | T2            | 0.17                  |
| MTCT rate during breastfeeding (newly infected)                | T3            | 0.29                  |
| Breastfeeding rate among mothers HIV+ at delivery              | B1            | 0.95                  |
| Breastfeeding rate among mothers HIV- at delivery              | B2            | 0.95                  |
| mortality among non-infected breastfed infants                 | M1            | 0.1                   |
| mortality among infected infants                               | M2            | 1                     |
| Relative risk of mortality of non-breastfed infants            | R             | 3                     |
| Duration of breastfeeding (years)                              | D             | 1                     |
| Incidence of new infections during breastfeeding period        | $I_D$         | $1-(1-I)^D$           |

Three mother-to-child HIV transmission rates are used, representing the transmission before and during delivery (T1), transmission through breastfeeding by a mother infected before delivery (T2), and transmission through breastfeeding by a mother newly infected after delivery (T3). Current methods of testing for HIV in infants do not permit the timing of transmission to be estimated with precision. The rate of transmission before and during delivery is therefore estimated from the rate of infection observed among infants of non-breastfeeding women. Because the prevalence of not breastfeeding is generally low in poor communities in developing countries, this rate is estimated mainly in affluent communities. In a large multi-center study in Europe, the transmission rate among 683 non-breastfed infants of mothers infected before delivery was 13.6% (European Collaborative Study, 1992) and in a French study of 801 infected non-breastfeeding mothers the rate was 19% (Mayaux et al., 1995). In the meta-analysis reported by Dunn et al. (1992), 16.1% of 1567 non-breastfeeding mothers in six studies transmitted the virus to their infants. Although the prevalence of not breastfeeding in poor communities is generally too low to permit reliable representative estimates of the equivalent rate under these conditions, evidence suggests that it is somewhat higher where malnutrition and other infections are more common (Bobat et al., 1996; Semba et al., 1994; Landers, 1996). The baseline value for T1 used in these analyses is 20%.

**Table 2.** Formulae to calculate the number of infant deaths in each of 9 mutually exclusive categories. Total deaths are calculated by summing across relevant categories. For symbol definitions, see Table 1.

| <b>Category</b>  | <b>Formula</b>                            |
|--|---|
| <b>AIDS deaths</b>   |   |
| 1. infected prior to delivery (pre- and intra-partum infections)               | $N * P * T1 * M2$                         |
| 2. infected via breastfeeding by mothers infected prior to delivery            | $N * P * (1-T1) * B1 * T2 * M2$           |
| 3. infected via breastfeeding by mothers infected after delivery               | $N * (1-P) * I_D * B2 * T3 * M2$          |
| <b>Non-AIDS deaths</b>   |   |
| 4. breastfed uninfected infants born to mothers infected prior to delivery     | $N * P * (1-T1) * B1 * (1-T2) * M1$       |
| 5. non-breastfed uninfected infants born to mothers infected prior to delivery | $N * P * (1-T1) * (1-B1) * M1 * R$        |
| 6. breastfed uninfected infants born to mothers infected after delivery        | $N * (1-P) * I_D * B2 * (1-T3) * M1$      |
| 7. non-breastfed uninfected infants born to mothers infected after delivery    | $N * (1-P) * I_D * (1-B2) * M1 * R$       |
| 8. breastfed infants born to uninfected mothers                                | $N * (1-P) * (1 - I_D) * B2 * M1$         |
| 9. non-breastfed infants born to uninfected mothers                            | $N * (1-P) * (1 - I_D) * (1-B2) * M1 * R$ |

In a meta-analysis of 6 studies Dunn et al. (1992) estimate the rate difference between breastfed and non-breastfed infants as 14 % (95% confidence interval = 7-22%). This is the *additional* percentage among the estimated 84% of infants uninfected at the time of delivery. The estimated risk for an individual infant uninfected at delivery is therefore 14/84 or 16.7%. The baseline value for T2 used in this analysis is 17%. The wide confidence interval, together with problems of possible selection bias, unrepresentative samples and short breastfeeding durations in these studies, suggests that this estimate should be considered imprecise.

The baseline value for T3, also taken from the same meta-analysis by Dunn et al. (1992), based on 42 mothers in 4 studies, is 29% (95% confidence interval = 16-42%).

The underlying infant mortality rate among breastfed infants (M1) can be estimated from historical values for IMR for a given country prior to the HIV epidemic or, if the HIV prevalence remains low, from current statistics. The average IMR for the 48 least developed countries was 109 in 1996 and 171 in 1960 (UNICEF, 1998). The baseline value used for these analyses is 100 per thousand live births (10%). The mortality rate among infected infants (M2) is assumed to be

100%. Although it is acknowledged that many infected infants may survive well beyond infancy, most will die before age 5 and, under current standards of care in poor countries, virtually all will die in childhood. By comparing the number of deaths among uninfected infants with AIDS deaths that may occur well beyond infancy, there is an inherent underestimation of the relative importance of death due to not breastfeeding. Although some studies have noted health benefits of breastfeeding beyond the first year, our ability to quantify the mortality impact beyond infancy is limited and the number of deaths involved is relatively small.

The risk of death due to artificial feeding has not been studied in the context of avoiding mother-to-child transmission of HIV. A number of observational studies have documented higher risks of death due to diarrhea and respiratory tract infections among non-breastfed infants (Victora et al., 1987, 1989, 1992; Yoon et al., 1995, 1996; Sachdev et al., 1991). Habicht et al. (1986, 1988) used data from Malaysia to examine the effect of not breastfeeding on infant death due to any cause. These authors took great pains in their analysis to address and avoid possible bias. In households with both a toilet and piped water, non-breastfed infants were 2.51 times more likely to die than breastfed infants were. This risk ratio increased to 2.67 in household without piped water and to 5.20 in households with neither a toilet nor piped water. The baseline value used here for the relative risk of death due to artificial feeding (R) is 3.0.

The model described treats both the underlying infant mortality rate and the relative risk of death due to artificial feeding as constant over the period of infancy. In fact, both of these are higher early in infancy and fall as the infant matures. One way of dealing with this changing situation is to examine a sequence of shorter periods throughout infancy. This is possible using this spreadsheet but would require virtually every variable to be re-estimated for each period in the sequence.

Breastfeeding rates are the key variable to be manipulated in the model. Given the substantial mortality risks associated with breastmilk substitutes under conditions of poverty and poor hygiene, policy makers, health workers involved in counseling HIV+ mothers and mothers themselves may want to know what circumstances favor breastmilk substitutes. This model allows manipulation of the breastfeeding rate among both infected (B1) and uninfected (B2) mothers to estimate the impact of different infant feeding strategies on transmission and overall risk of infant mortality due to any cause. In the baseline scenario it is assumed that 95% of all mothers breastfeed.

### ***Critical Values***

A “critical value” is the value of a variable in the model that results in an ambiguous result. When the variable is equal to its critical value, the estimated mortality for one infant feeding strategy is the same as for another. The policy implications are therefore ambiguous. No strategy can be recommended above the other. For example, given the levels of other assumptions in the model, a policy analyst might want to know at what level of R (the relative risk of mortality due to not breastfeeding) a proposed policy would be called into question. When the relative risk is lower than its critical value, breastmilk substitutes are safer than breastfeeding. When it is higher, breastfeeding is safer. Given a plausible range for R, the critical value thus provides guidance on how much confidence should be placed in the current policy. It can also be used as a goal for counselors and health professionals who are challenged to reduce the risk of breastmilk substitutes so that they *are* safer than breastfeeding by the infected mother. Similarly, holding

other variables constant, the critical value for the IMR (M1) would indicate a level below which conditions generally favor the use of breastmilk substitutes over breastfeeding by a mother infected with HIV.

Although the transmission rate is less subject to policy influence it is an important but imprecisely known policy determinant. A comparison of its critical value with the plausible range of values currently used is therefore informative.

Formulas for critical values are easily derived from those used to calculate survival in each category (Table 1). Only categories describing infected mothers are used because we know that breastfeeding among uninfected mothers is unambiguously beneficial. Taking just the categories representing mothers infected before delivery (1, 2, 4, and 5), and solving the equality  $Deaths_{B1=1} = Deaths_{B1=0}$  for single variables we get:

$$T2_{cv} = (M1 * (R - 1)) / (M2 - M1)$$

$$M1_{cv} = (T2 * M2) / (T2 + (R - 1))$$

$$R_{cv} = ((T2 * M2) + ((1-T2) * M1)) / M1$$

(see Technical Appendix for details).

A question related to the spillover phenomenon concerns the situation when most or all mothers do not know their status because testing is either not available or not generally used. Under such conditions, policy makers may wish to know what universally recommended infant feeding strategy would result in the lowest infant mortality rates. One way of addressing this question is to determine the HIV prevalence that would render the universal promotion of breastmilk substitutes among all women in the population a safer strategy than universal breastfeeding. The answer varies according to the relative risk and the IMR. This is a “critical value” problem that involves solving the equation  $Deaths_{B1=B2=1} = Deaths_{B1=B2=0}$  for prevalence when the other variables in the model are held constant. By substituting these values of B1 and B2 and solving for P (see Technical Appendix for details), we get:

$$P = \frac{(M1 * ((I_D * T3) - 1 + R)) - (M2 * I_D * T3)}{(M2 * ((T2 * (1 - T1)) - (I_D * T3))) + (M1 * ((T2 * (T1 - 1)) + (T1 * (R - 1)) + (I_D * T3)))}$$

This solution is a simplification of the true  $P_{cv}$  because it assumes that  $I_D$  is a constant where in fact it is related to P. Under stable conditions, I is approximately equal to  $P/d$  where d is the duration from infection to death. The above equation will provide a good estimate of  $P_{cv}$  if I is pre-chosen to approximate  $P_{cv}/d$ . For the estimates of  $P_{cv}$  presented here, an iterative method is used to estimate I, using  $I = P_{cv}/d$  based on seed estimates of  $P_{cv}$  and assuming  $d=7$  years (see Appendix). Actual risk of infection in the year following birth may be lower, if abstinence is observed for a period following delivery, or higher, if this results in the male partner having high risk sex with other partners.

## Results

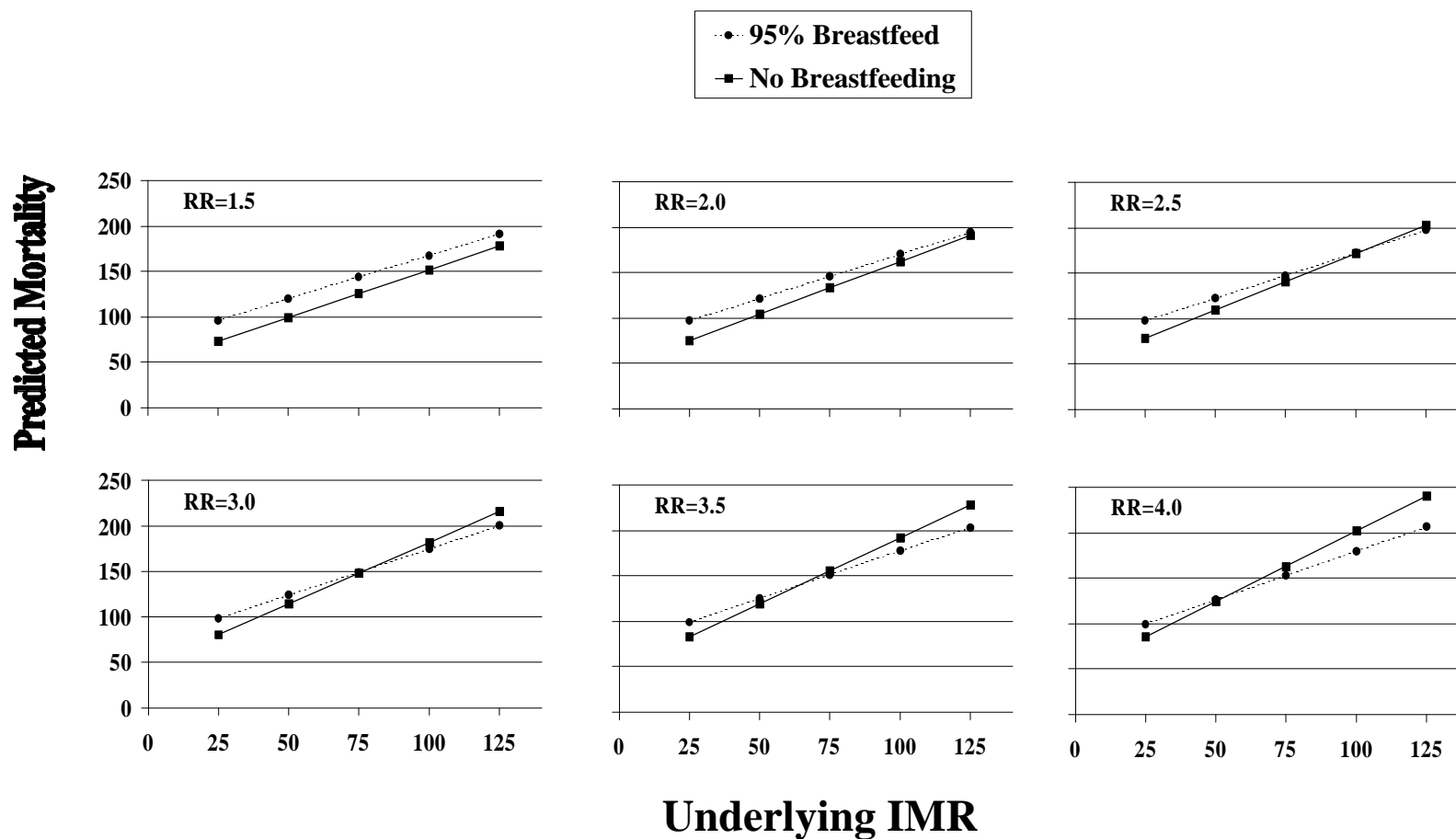
### *Effects of Not Breastfeeding among HIV-positive Mothers*

The model can be used to compare the risk of mother-to-child transmission of HIV with the risk of death due to not breastfeeding. For this comparative analysis, the breastfeeding rate for HIV-infected mothers is set at either 95% or zero. Although a zero rate is not realistic at the population level, it provides a convenient basis for comparing infant feeding strategies. The comparison outcome is total mortality. Holding other baseline values constant, this analysis was repeated over a range of infant mortality rates from 25 to 125/1000 and for a range of relative risks from 1.5 to 4.0. The results, presented in Table 3 and illustrated in Figure 2, show how the underlying IMR and the relative risk jointly determine which infant feeding strategy is safest. If the relative risk is 2 or lower, use of breastmilk substitutes is safer over the entire range of IMRs examined. If the relative risk is 3 (the baseline value), then breastfeeding is safer at IMRs greater than 75. As the relative risk and the underlying IMR increase so does the survival advantage of breastfeeding.

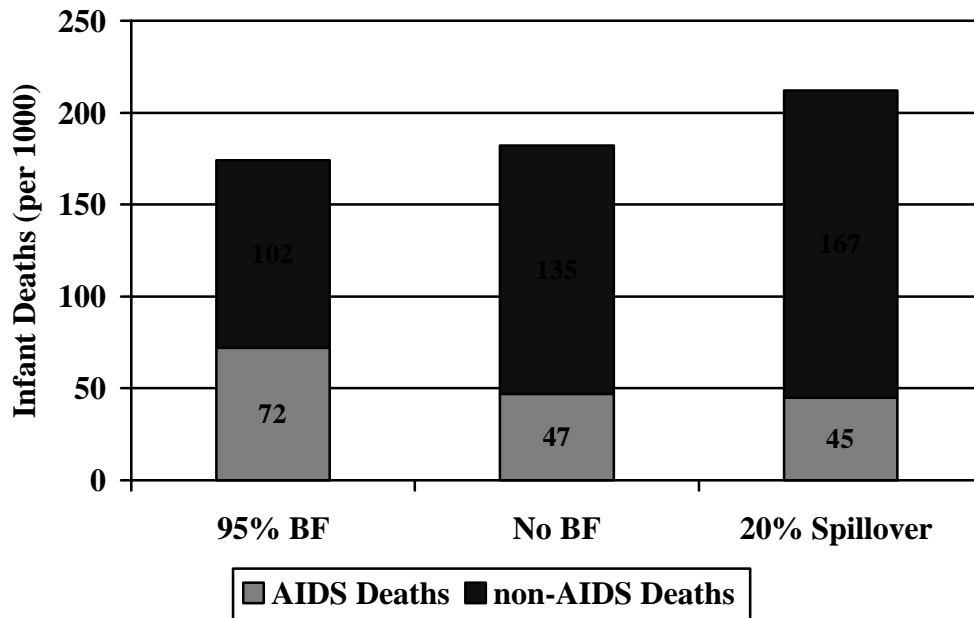
**Table 3.** Predicted total number of infant deaths (among a cohort of 1000 live births) when 95% or 0% of infected mothers breastfeed, as a function of the relative risk of death due to not breastfeeding and the underlying IMR. It is assumed that 95% of uninfected mothers breastfeed. Other assumptions are also as described in Table 2.

|            | Relative Risk |     |         |     |         |     |         |     |         |     |         |     |
|------------|---------------|-----|---------|-----|---------|-----|---------|-----|---------|-----|---------|-----|
|            | 1.5           |     | 2       |     | 2.5     |     | 3       |     | 3.5     |     | 4       |     |
|            | BF rate       |     | BF rate |     | BF rate |     | BF rate |     | BF rate |     | BF rate |     |
| IMR        | 95%           | 0%  | 95%     | 0%  | 95%     | 0%  | 95%     | 0%  | 95%     | 0%  | 95%     | 0%  |
| <b>25</b>  | 96            | 73  | 97      | 75  | 97      | 78  | 98      | 80  | 99      | 83  | 99      | 85  |
| <b>50</b>  | 120           | 99  | 121     | 104 | 122     | 109 | 124     | 114 | 125     | 119 | 126     | 124 |
| <b>75</b>  | 144           | 126 | 146     | 133 | 147     | 141 | 149     | 148 | 151     | 156 | 153     | 163 |
| <b>100</b> | 168           | 152 | 170     | 162 | 172     | 172 | 175     | 182 | 177     | 192 | 180     | 202 |
| <b>125</b> | 191           | 178 | 194     | 191 | 197     | 203 | 200     | 216 | 203     | 228 | 206     | 241 |

**Figure 2.** Predicted total mortality as a function of underlying infant mortality rate (IMR) at different assumed relative risks (RR) of death due to not breastfeeding, for a situation where either 95% or 0% of HIV+ mothers breastfeed. The assumed prevalence of HIV among pregnant women is 20%. Breastfeeding is a safer infant feeding strategy when the relative risk and underlying IMR are high. Other assumptions are as described in Table 2.



**Figure 3.** AIDS and non-AIDS deaths among infants under different infant feeding strategies: when 95% of infected mothers breastfeed (95% BF) and when none breastfeed (no BF). For this simulation it is assumed that the prevalence is 20%, the relative risk of death due to not breastfeeding is 3.0 and 17% of infants uninfected at delivery who are breastfed by an infected mother will become infected. Other assumptions are as described in Table 2. Under these conditions, not breastfeeding would result in 4% more infant deaths. Also shown are the additional effects of a 20 percentage point reduction (from 95% to 75%) among uninfected mothers (20% spillover), assuming that all infected mother do not breastfeed. This would result in an additional 17% increase in overall mortality.



Given the baseline assumptions (relative risk of 3 and underlying IMR of 100), breastmilk substitutes (0% breastfeeding) would result in greater overall mortality. Although AIDS deaths would be reduced (from 72 to 47 per 1000 live births) there would be a greater increase in the number of non-AIDS deaths. The total effect would be an increase in mortality from 175 to 182. These results are illustrated in Figure 3.

***Effects of Spillover: Use of Breastmilk Substitutes among Uninfected Mothers***

There is concern that the promotion of breastmilk substitutes among HIV+ mothers may lead mothers who do not know their status but who suspect that they are infected, to use substitutes or otherwise to modify their infant feeding strategy to reduce the risk of transmission. The effects of such “spillover” on infant health and survival are simulated using the spreadsheet model by assuming a reduction in breastfeeding rates among uninfected mothers. The net impact of such spillover depends on the underlying IMR, the HIV prevalence and the degree of spillover. However, since the *direction* of the effect does not depend on the degree of spillover, the simulation here assumes a constant spillover of 20 percentage points (comparing the baseline

**Table 4.** Predicted excess number of infant deaths (among a cohort of 1000 live births) due to a reduction in breastfeeding rates from 95% to 75% among uninfected mothers, as a function of the prevalence of HIV among pregnant women and the underlying IMR. It is assumed that infected mothers do not breastfeed. Other assumptions are as described in Table 2.

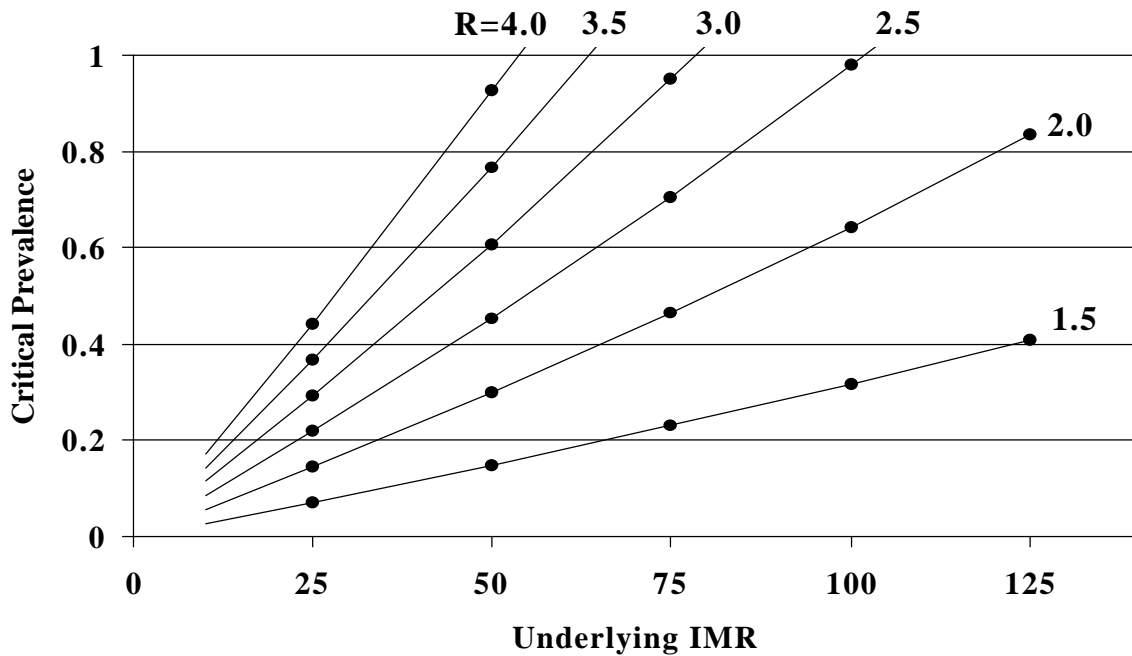
| IMR        | HIV Prevalence (%) |    |    |    |    |    |
|------------|--------------------|----|----|----|----|----|
|            | 2                  | 5  | 10 | 20 | 30 | 40 |
| <b>25</b>  | 10                 | 9  | 8  | 7  | 5  | 4  |
| <b>50</b>  | 19                 | 19 | 17 | 15 | 12 | 10 |
| <b>75</b>  | 29                 | 28 | 26 | 23 | 19 | 16 |
| <b>100</b> | 39                 | 38 | 35 | 31 | 26 | 22 |
| <b>125</b> | 49                 | 47 | 44 | 39 | 33 | 28 |

scenario rate of 95% breastfeeding among uninfected mothers with a 75% rate due to spillover). Total expected infant mortality is calculated with and without spillover over a range of prevalences and IMRs. The results, presented in Table 4, show the negative effects of spillover at all IMRs and HIV prevalences. The number of infant deaths due to spillover increases directly with the underlying IMR. A given degree of spillover will result in more infant deaths when HIV prevalence is lower, simply because it will affect more uninfected mothers. Using the baseline assumptions (IMR of 100 and HIV prevalence of 20%), the effect of a reduction in breastfeeding rates among uninfected mothers from 95% to 75% would be a 17% increase in overall mortality, from 182 to 212 deaths per thousand live births (Figure 3).

***Effects of Different Infant Feeding Strategies among Mothers of Unknown Status***

If the mother’s status is not known, the safest infant feeding strategy will depend on the same key variables as for the mother who is known to be infected, namely the underlying IMR, the relative risk of death due to artificial feeding and the risk of transmission through breastfeeding. In addition, since the mother’s actual status is not known, the risk analysis requires some assessment of the probability that she is infected. Without any other information this probability may be estimated as the prevalence of HIV in the population. A better estimate may be available if the prevalence is known for the population subgroup to which the mother belongs (e.g., pregnant women). The model can be used to test the safety of different infant feeding strategies by comparing total mortality under different conditions when all mothers breastfeed with that when none do. This can be repeated for different population prevalences. Under some conditions, there will be a prevalence at which both infant feeding strategies (breastfeeding and artificial feeding) result in the same total mortality. When HIV prevalence is lower than this, less mortality would be observed if all mothers of unknown status breastfed. At higher prevalence it would be safer if all fed artificially. Under some conditions of high underlying mortality and high risk of death due to artificial feeding, this critical prevalence is equal to or greater than 1, meaning that it is safer to breastfeed regardless of the mother’s HIV status.

**Figure 4.** HIV prevalence at which breastfeeding by all mothers would result in the same overall mortality as not breastfeeding by all mothers, regardless of HIV status. This “critical prevalence” is graphed as a function of the underlying infant mortality rate (IMR) and the relative risk of death due to not breastfeeding. Other assumptions are as described in Table 2. A universal policy of discouraging breastfeeding would result in lower overall mortality only when the HIV prevalence is high and both the underlying IMR and relative risk are low, a combination of conditions that does not generally exist. Even when the underlying IMR is 25 and the relative risk is 1.5, universal use of breastmilk substitutes would be advised only if the prevalence exceeds 7.2%. Under the baseline conditions (IMR=100, R=3), the critical prevalence is greater than 1, meaning that even if all mothers were infected, universal breastfeeding would result in lower overall mortality than universal use of substitutes.



The HIV prevalence at which breastfeeding by all mothers would result in the same overall mortality as not breastfeeding by all mothers, regardless of HIV status, is presented in Table 5 and illustrated in Figure 4. This “critical” prevalence increases with the underlying infant mortality rate (IMR) and the relative risk of death due to not breastfeeding. Other variables in the model are the same as the baseline values presented in Table 2. Results suggest that use of breastmilk substitutes among all mothers, regardless of HIV status, would result in lower overall mortality only when the HIV prevalence is high and both the underlying IMR and relative risk are low, a combination of conditions that does not generally exist. For example, even when the underlying IMR is 25 and the relative risk is 1.5, universal use of breastmilk substitutes would only be advised if the prevalence exceeds 7.2%. Under the baseline conditions (IMR=100, relative risk=3), the critical prevalence is greater than 100%, meaning that even if all mothers were infected, universal breastfeeding would result in lower overall mortality than universal use of breastmilk substitutes.

**Table 5.** Critical HIV prevalence at which breastfeeding by all mothers would result in the same overall mortality as use of breastmilk substitutes by all mothers, regardless of HIV status, as a function of the relative risk of death due to not breastfeeding and the underlying IMR. Other assumptions are as described in Table 2. If the critical prevalence is greater than 1, this means that even if all mothers are infected, the safer strategy is to breastfeed.

| IMR | Relative Risk |       |       |       |       |       |
|-----|---------------|-------|-------|-------|-------|-------|
|     | 1.5           | 2.0   | 2.5   | 3.0   | 3.5   | 4.0   |
| 10  | 0.028         | 0.057 | 0.086 | 0.114 | 0.143 | 0.172 |
| 25  | 0.072         | 0.145 | 0.218 | 0.292 | 0.366 | 0.441 |
| 50  | 0.149         | 0.300 | 0.452 | 0.607 | 0.765 | 0.925 |
| 75  | 0.230         | 0.465 | 0.705 | 0.951 | >1    | >1    |
| 100 | 0.317         | 0.642 | 0.979 | >1    | >1    | >1    |
| 125 | 0.409         | 0.833 | >1    | >1    | >1    | >1    |

### ***Critical Values***

Substituting the baseline values from Table 2 into these formulae, the critical values are:

$$T2_{cv} = (0.1 * (3 - 1)) / (1 - 0.1) = 0.222$$

$$M1_{cv} = (0.17 * 1) / (0.17 + (3 - 1)) = 0.0783$$

$$R_{cv} = ((0.17 * 1) + ((1-0.17) * 0.1)) / 0.1 = 2.53$$

This means that if the actual transmission rate was 22.2% (rather than 17%), or the underlying IMR among breastfed infants was 78.3 (rather than 100) per thousand live births, or the non-breastfed infant was 2.53 (rather than 3) times more likely to die, the estimated risk of death would be the same whether the infant (born uninfected to an infected mother) was breastfed or not. Policy analysts can use these formulas or the spreadsheet itself to calculate critical values reflecting other specific situations.

## **Discussion**

### ***Optimal Infant Feeding Strategy***

In some situations, not breastfeeding may act as a signal to the mother’s family and community that she is infected. Announcing her status in this way may result in stigmatization and social ostracization (including, in extreme cases, violence, rejection and destitution). Ultimately it is the mother who decides how to feed her infant, based on her own evaluation of these and other risks not considered by the model. The purpose of the model is to assess only risks of mother-to-child transmission vs. the risk of death due to artificial feeding. This analysis should be used to inform decisions but it is recognized that other criteria and considerations may lead to “optimal”

policies, programs and individual infant feeding decisions that are different from those suggested by this analysis.

This model suggests that under conditions of high infant mortality the risk of infant death due to artificial feeding is greater than the risk of mother-to-child transmission due to breastfeeding. The estimated relative risk of death due to artificial feeding is based on observational studies that compare the survival of breastfed and non-breastfed infants. In these studies mothers have chosen to feed a breastmilk substitute for reasons other than fear of transmission of HIV. Although we have no way of knowing what the motivation for using breastmilk substitutes was in each case, we know at least that this decision was not driven by fear of HIV infection. Mothers who choose breastmilk substitutes to reduce the risk of transmission of HIV may not be as well situated to afford breastmilk substitutes feeding or to provide them safely. The relative risks in the literature that are derived from mothers who chose substitutes under happier circumstances may therefore underestimate the risks of breastmilk substitutes when chosen to reduce the risk of transmission of HIV.

On the other hand, the risk of death due to artificial feeding in specific settings is not necessarily fixed. Although she cannot fully compensate for the inferiority of artificial feeding, a mother who decides not to breastfeed can improve the survival chances of her infant by taking steps to ensure the nutritional adequacy of the replacement diet and to reduce contamination. In the event that the infant becomes ill, timely and adequate health care can reduce the risk of death. The role of the health worker is to support the mother by providing the counseling and care needed to make her choice of infant feeding method as safe as possible. The value chosen for the relative risk in the model should reflect the expected effects of such attenuating efforts.

### *Spillover*

Spillover is a difficult effect to model because we have no empirical indication of how great the spillover effect might be in different situations or what form it would take. The forces shaping the infant feeding strategy of the mother who does not know her status but who suspects that she may be infected are complex. They include the mother's perception of her own risk of infection, her perception of the risk of transmission, and the perceived costs and benefits of not breastfeeding (including stigmatization of non-breastfeeding mothers as infected). Thus until there are better empirical indications of what degree of spillover can be expected under different conditions, the estimates presented here are speculative. Their direction however, is not.

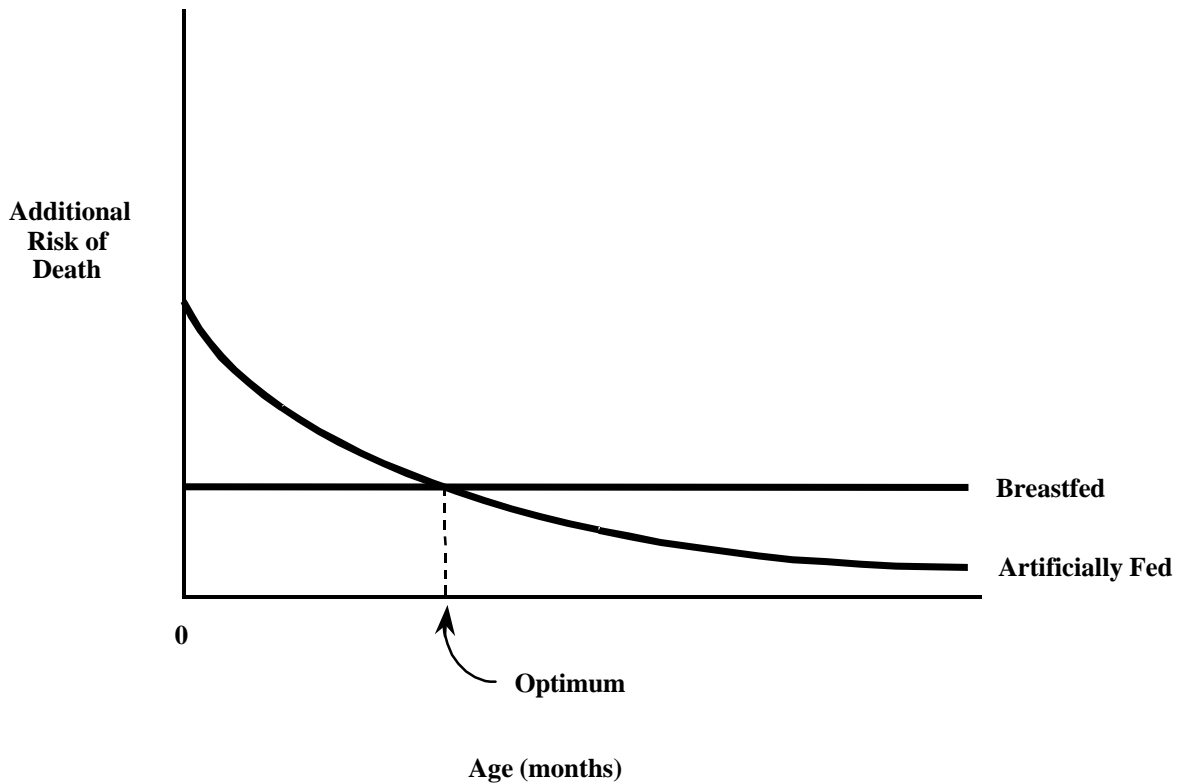
### *Mothers of Unknown Status*

The vast majority of mothers do not know their HIV status. When applied to these women the risk analysis suggests that breastfeeding is virtually always the safest infant feeding strategy. The only situation where use of breastmilk substitutes would be expected to improve child survival is where the prevalence of HIV is high and the risk of death due to artificial feeding is low, a combination of conditions that do not generally exist.

### *An Optimal Time to Stop Breastfeeding?*

The analytical method described here covers the entire first year of life. It may also be of interest to address narrower periods throughout infancy in turn. The decision to initiate breastfeeding

**Figure 5.** Schematic illustration of the changing balance of additional risks of death due to artificial feeding vs the risk of mother-to-child transmission of HIV through breastfeeding. The age at which the risk of death due to artificial feeding falls below the risk of transmission would be the optimal age to begin using a replacement diet.



may be made on the basis of a risk assessment covering just the first few months. The relative risk of death due to artificial feeding is reduced as the infant ages whereas, as far as we know, the risk of transmission remains relatively constant. This situation is illustrated in Figure 5. As the infant matures and the risk of death due to artificial feeding is reduced, the balance of risks may shift to favor an alternative diet. The optimal timing of introduction of an alternative diet occurs at the age when this shift occurs. Although this is shown to occur about 4 months in Figure 5, the actual optimal time to stop breastfeeding would vary with the situation, depending on the shape and location of the replacement diet risk curve, which are unknown. If underlying mortality rates and the risks associated with the alternative diet can be estimated, the risk analysis model can be used to assess the safety of different feeding strategies for any interval.

### **Acknowledgements**

This paper has benefited from the useful comments of Chessa Lutter, Elizabeth Preble and Ellen Piwoz.

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## Technical Appendix: Calculation of Critical Values

Formulas for critical values can be derived from those presented in Table 1. These pertain to mothers known to be infected. Taking just the categories representing mothers infected before delivery (categories 1, 2, 4, and 5 in Table 1), total deaths are represented as:

$$\text{Deaths} = (N * P * T1 * M2) + (N * P * (1-T1) * B1 * T2 * M2) + (N * P * (1-T1) * B1 * (1-T2) * M1) + (N * P * (1-T1) * (1-B1) * M1 * R)$$

The critical value is derived by solving the equality  $\text{Deaths}_{B1=1} = \text{Deaths}_{B1=0}$ , for any single variable in the formula. By substituting these values of B1 into the equality  $\text{Deaths}_{B1=1} = \text{Deaths}_{B1=0}$ , whole terms drop out because they contain zero as a multiplier:

$$\text{Deaths}_{B1=1} = \text{Deaths}_{B1=0}$$

substituting:

$$(N * P * T1 * M2) + (N * P * (1-T1) * 1 * T2 * M2) + (N * P * (1-T1) * 1 * (1-T2) * M1) + (N * P * (1-T1) * (1-1) * M1 * R) = (N * P * T1 * M2) + (N * P * (1-T1) * 0 * T2 * M2) + (N * P * (1-T1) * 0 * (1-T2) * M1) + (N * P * (1-T1) * (1-0) * M1 * R)$$

removing terms containing zero as multiplier:

$$(N * P * T1 * M2) + (N * P * (1-T1) * 1 * T2 * M2) + (N * P * (1-T1) * 1 * (1-T2) * M1) = (N * P * T1 * M2) + (N * P * (1-T1) * (1-0) * M1 * R)$$

simplifying:

$$(T2 * M2) + ((1-T2) * M1) = M1 * R$$

solving for T2, M1 and R:

$$T2_{cv} = (M1 * (R - 1)) / (M2 - M1)$$

$$M1_{cv} = (T2 * M2) / (T2 + (R - 1))$$

$$R_{cv} = ((T2 * M2) + ((1-T2) * M1)) / M1$$

Finding the prevalence at which breastfeeding by all mothers would result in the same level of risk as use of breastmilk substitutes by all mothers is more complicated than the previous critical value calculations because it includes all the categories listed in Table 1. Nevertheless, the principles are the same:

$$\text{Total Deaths}_{B1=B2=1} = \text{Total Deaths}_{B1=B2=0}$$

Substituting:

$$\begin{aligned} &(N * P * T1 * M2) + \\ &(N * P * (1-T1) * 1 * T2 * M2) + \\ &(N * (1-P) * I_D * 1 * T3 * M2) + \\ &(N * P * (1-T1) * 1 * (1-T2) * M1) + \\ &(N * P * (1-T1) * 0 * M1 * R) + \end{aligned}$$

$$\begin{aligned}
& (N * (1-P) * I_D * 1 * (1-T3)* M1) + \\
& (N * (1-P) * I_D * 0 * M1 * R) + \\
& (N * (1-P) * (1- I_D) * 1 * M1) + \\
& (N * (1-P) * (1- I_D) * 0 * M1 * R) \\
= & \\
& (N * P * T1 * M2) + \\
& (N * P * (1-T1) * 0 * T2 * M2) + \\
& (N * (1-P) * I_D * 0 * T3 * M2) + \\
& (N * P * (1-T1) * 0 * (1-T2) * M1) + \\
& (N * P * (1-T1) * 1 * M1 * R) + \\
& (N * (1-P) * I_D * 0 * (1-T3)* M1) + \\
& (N * (1-P) * I_D * 1 * M1 * R) + \\
& (N * (1-P) * (1- I_D) * 0 * M1) + \\
& (N * (1-P) * (1- I_D) * 1 * M1 * R)
\end{aligned}$$

Removing zero terms and dividing both sides by N:

$$(P * (1-T1) * T2 * M2) + ((1-P) * I_D * T3 * M2) + (P * (1-T1) * (1-T2) * M1) + ((1-P) * I_D * (1-T3)* M1) + ((1-P) * (1- I_D) * M1) = (P * (1-T1) * M1 * R) + ((1-P) * C * M1 * R) + ((1-P) * (1- I_D) * M1 * R)$$

Simplifying further:

$$(P*((M2*((T2*(1-T1))-(I_D *T3)))+(M1*((T2*(T1-1))-T1+(I_D *T3))))+(M2* I_D *T3)+(M1*(1-(I_D *T3))) = R*M1*(1-(P*T1))$$

Solving for P:

$$P = \frac{(M1*((I_D *T3) - 1 + R)) - (M2 * I_D * T3)}{(M2 * ((T2 * (1 - T1)) - (I_D * T3))) + (M1 * ((T2 * (T1 - 1)) + (T1 * (R - 1)) + (I_D * T3)))}$$

This formula does not account for the relationship between the annual incidence of new infections (I) and the HIV prevalence (P). If the value of I is chosen judiciously to approximate the actual incidence at the predicted critical value of P, this formula will provide an accurate estimate. Under stable conditions, I is approximately equal to P/d where d is the duration from infection to death. The above equation will provide a good estimate of P if I is chosen to approximate  $P_{cv}/d$ . A consistent and precise iterative method (used here) begins with a seed value of  $P_{cv}$  and estimates  $I = P_{cv}/d$ .  $P_{cv}$  can then be estimated using this value of I and I recalculated base on the new estimate of  $P_{cv}$ . Stable estimates of  $P_{cv}$  can be obtained within 2 or 3 iterations.

In some cases, where the underlying infant mortality rate and the relative risk of death due to artificial feeding are high, P calculated using this formula may exceed 1. This means that under these conditions, even if a mother is infected (prevalence=100%), her infant's risk of death is lower if she breastfeeds.