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Bayesian estimation of the time-varying sensitivity of a diagnostic test with application to mother-to-child transmission of HIV

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Summary

We present a Bayesian model to estimate the time-varying sensitivity of a diagnostic assay when the assay is given repeatedly over time, disease status is changing and the gold standard is only partially observed. The model relies on parametric assumptions for the distribution of the latent time of disease onset and the time-varying sensitivity. Additionally, we illustrate the incorporation of historical data for constructing prior distributions. We apply the new methods to data collected in a study of mother-to-child transmission of HIV and include a covariate for sensitivity to assess whether two different assays have different sensitivity profiles.

Keywords

Bayesian models; mother-to-child transmission of HIV; Time-varying sensitivity

1. Introduction

Because infants have maternal antibodies circulating in their bloodstream, an infant's HIV infection status cannot be ascertained by antibody assays. Instead, HIV RNA or DNA PCR assays are used to detect HIV infection. However, early in the disease process, there may not be adequate circulating virus to be detected by the PCR assays resulting in false negatives. Early studies to estimate the sensitivity and specificity of various PCR assays were conducted in non-breastfeeding populations where a gold standard was observable after sufficient follow-up because infants were no longer at risk for HIV transmission after birth. However, in breastfeeding populations, infants who were not infected in utero or during delivery continue to be at risk for HIV transmission throughout the duration of breastfeeding. In these populations, a gold standard is only partially observable. In this paper, we present a new model for estimating the time-varying sensitivity of a diagnostic assay when the gold standard is only partially observed.

An interest in understanding the relative sensitivities of two HIV-1 viral assays to detect HIV-1 infection in HPTN 024 (Taha et al., 2006), a multi-site double blinded placebo controlled trial of antibiotics to prevent perinatal mother-to-child transmission (MTCT) of HIV conducted in Zambia, Malawi and Tanzania, motivated this research. In clinical trials to prevent perinatal MTCT, mothers are usually randomized to an intervention that may be received either by the mother, the infant or both. Infants are tested on a schedule with the

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Supplementary Materials
Web Appendices 1–3 are available under the Paper Information link at the Biometrics website http://www.tibs.org/biometrics.

first test usually occurring at birth and a second test occurring between 4 and 8 weeks. Subsequent visits are also scheduled to evaluate late postnatal MTCT of HIV-1 via breast milk (transmission first detected after 6 weeks) and mortality. Specifically in HPTN 024, these visits were scheduled at 3, 6, 9 and 12 months.

Several researchers have estimated the time-varying sensitivity of DNA and RNA assays in infants who are not breastfed and whose infection status at birth is known after sufficient follow-up (Figure 1). Young et al. (2000) found that the DNA PCR assay had a sensitivity of 38% at birth and 100% at two months in a group of 53 infected infants from a clinical trial in Thailand. They also estimated the sensitivity of an RNA PCR test to be 47% at birth and 100% at 2 months in the same group of infants. Dunn et al. (2000) estimated the sensitivity of a DNA PCR assay in participants from a group of clinical trials in the United States and Europe to be 36% at birth. Among those infants who had a false negative test at birth, the median time to viral detectability was 14.8 days. Simonds et al. (1998) estimated the sensitivity of a qualitative RNA PCR test to be 38% at birth. Nesheim et al. (2003) estimated the time-varying sensitivity of quantitative RNA tests in 156 infants in the United States to be 29% at birth 79% at 8–28 days 91% at 29–60 days, 96% at 61–120 days and 97% at 120–180 days. The results from these studies are plotted against time in Figure 1 and suggest a fairly low sensitivity at birth for detecting infections that occured in utero and during labor and delivery. However, the sensitivity increases rapidly after birth.

Estimating the sensitivity and specificity of HIV diagnostic assays is not straight-forward in the presence of breastfeeding which exposes the infant to HIV after birth. Many infants will acquire HIV-1 postnatally and may have a combination of true and false negative and true positive test results. In these populations, we may determine an infant's true infection status over time if s/he tests negative according to some gold standard test (like an antibody assay) or if s/he tests positive consistently from birth. Infection status at time points after birth is difficult to ascertain in infants who have their first positive test result after a negative test result. For example, if an infant has a negative test result at birth, a positive test result at six weeks and is breastfed, it is unknown whether the infection happened in the in utero/ intrapartum period (false negative at birth) or via breastfeeding (true negative at birth).

There has been extensive literature on estimating sensitivity and specificity of diagnostic tests without a gold standard at a point in time. Most of the focus has been on latent class analysis and required at least two types of diagnostic tests be performed. Hui and Zhou (1998) provide an overview of early work in evaluating diagnostic tests with missing or imperfect gold standards. Most of this work focuses on correctly specifiying the covariance of different diagnostic tests. Recent advances have focused on relaxing the number of different tests required (Dendukuri and Joseph, 2001) and adapting error models to better reflect biology (Albert et al., 2001) and examing the robustness of the latent class models to model assumptions (Albert and Dodd, 2004). Only Espeland et al. (1989) consider multiple diangostic tests over time with incident disease.

Several authors have proposed methods to adjust for imprefect HIV-1 diagnostic assays in infants. Balasubramanian and Lagakos (2001) proposed semi-parametric models for estimating the timing of MTCT of HIV that occurs in utero and during delivery in a non-breastfeeding population. They used both linear and step functions to model the dependence of sensitivity on time. Subsequently, Balasubramanian and Lagakos (2003) developed a model for time to an event when assays are imperfect and illustrate the method in a study of MTCT of HIV in a breastfeeding population. Their models rely on correct specification of time-dependent sensitivity and assume 100% specificity. Zhang and Lagakos (2008) developed a model for timing of MTCT of HIV that allows for time-invariant imperfect sensitivity and specificity which they set at 0.95 and 0.99, respectively. Gupte et al. (2007)

proposed a comprehensive model for timing of MTCT of HIV that acounts for and estimates imperfect sensitivity by assuming an exponential model for sensitivity over time with means dependent on the mode of transmission. They grouped event times around the visit schedule and assumed an exponential distribution for the timing of breastmilk transmission.

We improve the model by Gupte et al. (2007) allowing for non-zero sensitivity at birth, adding covariates for estimating sensitivity, allowing continuous instead of grouped testing times, using a more flexible distribution for time to infection and incorporating prior information. The paper proceeds as follows. First, we present the model for time-varying sensitivity. Next we present the model for timing of transmission. In the Application, we elicit priors from historical studies where sensitivity was estimated in the absence of breastfeeding. Using follow-up HIV testing on infants from HIVNET 024, we estimate the sensitivity of two HIV assays used to assess the infection status of infants. We conclude with a discussion.

2. Methods

2.1 Modeling sensitivity

Before presenting the time-varying sensitivity model, we first introduce some notation. For the ith, $i = 1, \ldots, N$, infant, we observe the outcomes of a series of HIV tests, $Y_{i1}, \ldots, Y_{im_i}$, at times $t_{i1}, \ldots, t_{im_i}$, where m_i denotes the number of tests administered to the ith infant. Let $Y_{ij} = 1$ if the ith infant's test is postive at time t_{ij} and 0 if it is negative. The ith infant's unobserved event time is denoted as s_i and $I\{s_i \leq t_{ij}\} = 1$ denotes that the infant is infected at time t_{ij}, where $I\{x\}$ is an indicator function that equals 1 if x is true and 0 otherwise. We set $s_i = 0$ for infants who are infected in utero/during delivery.

PCR assays quantify the concentration of the HIV-1 virus circulating in the infant's bloodstream and have a lower limit of detection. If circulating viral levels are below this limit, the assay produces a false negative result. Early in infection, viral levels are too low to be detected, and, as time progresses, viral levels increase to detectable levels and the assay shows a positive result. Although sensitivity is a function of the amount of virus circulating in the infant's bloodstream, this information is not available to us. However, mathematical models tell us that viral levels in untreated individuals increase over time (Perelson and Nelson, 1999); therefore, we model sensitivity as a function of time and assume that the time between infection and detection follows an exponential distribution such that the sensitivity of the assay at time t_{ij} can be described as $\alpha(t_{ij}) = 1 - \exp(-e^{\omega X_{ij}}(t_{ij} - s_i)_+)$ where ω is a vector of parameters linking the potentially time-varying covariates, X_{ij} to the sensitivity and u_+ equals u if u is positive and zero otherwise.

It is possible that the initial levels of circulating virus or subsequent rates of viral replication are dependent on the mode of transmission (breastfeeding versus in utero/delivery) (Rouet et al., 2003), resulting in a sensitivity profile over time that is also dependent on the mode of transmission. Therefore, we extend the model for sensitivity to reflect this possibility as follows. First, to permit a non-zero sensitivity at birth, we introduce a parameter, $\tau_0 > 0$, that represents a time origin prior to birth for infants infected in utero/delivery and is measured in the same time units as the event time. The time-dependent model for sensitivity of an infant's HIV assay at time, t_{ij}, is then

$$\alpha(t_{ij}) = 1 - \exp[-\exp(\omega_0 + \omega_1 I\{s_i > 0\} + \omega_2 x_{1ij} + \cdots + \omega_p x_{p-1,ij}(t_{ij} - s_i + \tau_0 I\{s_i = 0\})_+], \quad (1)$$

where $x_1, \ldots, x_{p-1}$ are potential covariates of interest that may vary with time such as the assay used at time t_{ij}. In (1), sensitivity depends on the mode of transmission through the parameters ω_1 and τ_0. According to this model, the mean age at detection of HIV-1 infection for an in utero/delivery transmission is $1/\exp(\omega_0 + \omega_2 x_{1ij} + \cdots + \omega_p x_{p-1,\,ij}) - \tau_0$ units of time. The corresponding mean time between infection and detection for breastfeeding transmissions is $1/\exp(\omega_0 + \omega_1 + \omega_2 x_{1ij} + \cdots + \omega_p x_{p-1,\,ij})$ units of time.

Assuming that given the true timing of infection, the test results are independent, we can write the probability mass function for the joint distribtution of the *i*th infant's test results conditional on the timing of infection, s_i as

$$p(Y_{i1}, \ldots, Y_{im_i} | s_i, t_{i1}, \ldots, t_{im_i}, \omega, \pi, \tau_0) = \prod_{j=1}^{m_i} \left[\pi^{Y_{ij} I\{s_i > t_{ij}\}} (1-\pi)^{(1-Y_{ij}) I\{s_i > t_{ij}\}} \alpha_{ij}^{Y_{ij} I\{s_i \le t_{ij}\}} (1-\alpha_{ij})^{(1-Y_{ij}) I\{s_i \le t_{ij}\}} \right], \tag{2}$$

where π is 1 minus the specificity and allows for false positives due to potential specimen mishandling errors. Here, s_i represents the time of infection barring the intervention of a competing risk which can either be death or weaning. When the competing risk is death an infant is lost to all follow-up. However, when the competing risk is weaning, the infant will continue to be tested though it is no longer at risk of infection. We propose a model that accounts for weaning in the sensitivity function. We rewrite Equation (2) conditional on the time of weaning, u_i, as

$$\begin{aligned} &p(Y_{i1}, \ldots, Y_{im_i} | s_i, u_i, t_{i1}, \ldots, t_{im_i}, \omega, \tau_0 \pi) \\ &= \prod_{j=1}^{m_i} \left[\pi^{Y_{ij} I\{s_i > t_{ij} \vee u_i < s_i\}} (1-\pi)^{(1-Y_{ij}) I\{s_i > t_{ij} \vee u_i < s_i\}} \alpha_{ij}^{Y_{ij} I\{s_i \le t_{ij} \wedge s_i < u_i\}} (1-\alpha_{ij})^{(1-Y_{ij}) I\{s_i \le t_{ij} \wedge s_i < u_i\}} \right], \end{aligned} \tag{3}$$

where $\vee$ and $\wedge$ represent union and intersection, respectively. Now, $I\{s_i \le t_{ij} \wedge s_i < u_i\}$ refines the definition of infected at time t_{ij} so that an infant who would have an expected time of infection less than t_{ij} is not counted as infected if s/he was weaned before the expected time of infection.

2.2 Specifying the distribution of time to HIV infection

In this section, we present a biologically plausible model for the distribution of time to MTCT of HIV. Our goal when modeling the time to infection is to predict the time-to-event as accurately as possible for determining true and false HIV diagnostic test results; therefore, we must account for the features of the infection timing distribution that are unique to MTCT of HIV. First, we expect a fraction of infants to be infected at birth, either in utero or during delivery. Second, we expect another fraction of the cohort to be infected via breast milk during the first year of life. Third, we expect that the majority of infants will not experience MTCT of HIV. To accomodate these features, we specify the distribution as a mixture of three distributions where each component reflects a potential mode of transmission (or lack of transmission). We specify the distribution of the *i*th infants's time to HIV infection as

$$f(s_i) = \delta_0(s_i) p_{1i} + f^*(s_i) p_{2i} I\{0 < s_i < t_c\} + \delta_\infty(s_i)(1 - p_{1i} - p_{2i}), \tag{4}$$

where $\delta_0(s_i)$ is a point mass at zero to reflect transmission in utero or during delivery. The mixing proportion, p_{1i}, measures the cumulative infection rate prior to birth. The next component, $f^*(s_i)p_{2i}$, represents infection via breastmilk where $f^*(s_i)$ is a continuous distribution with support $(0, t_c)$, where t_c is the known end of the late postnatal transmission period defined either by weaning or end of study follow-up, and p_{2i} is the mixing proportion corresponding to $f^*(s_i)$. The third component, $\delta_\infty(s_i)(1 - p_{1i} - p_{2i})$, represents the probability that an infant does not acquire HIV from his mother. Without loss of generality, we assign an infection time of ∞ for these infants. The proportion of infants HIV-free at t_c is $1 - p_{1i} - p_{2i}$.

To accurately estimate transmission time as accurately as possible given the observed data, we include all known predictors of timing of transmission in the model. These predictors can be incorporated through regression on the survival times or the hazard and on the mixing probabilities. Let Z_i be a vector of covariates of length m_Z that are known to be associated with time to infection. Regression on the mixing probabilities for each component can be dependent on the entire vector of covariates, Z_i, or a subset of Z_i. For expository purposes and without loss of generality, we will assume that all the covariates in Z_i will be used to predict all the components of the model. We use the following regression models for the mixing probabilities;

$$\text{logit}(p_{1i}+p_{2i})=Z_i'\eta \tag{5}$$

and

$$\text{logit}\left(\frac{p_{1i}}{p_{1i}+p_{2i}}\right)=Z_i'\theta \tag{6}$$

where η is a vector of length m_Z linking the covariate vector Z_i to the risk of mother to child transmission of HIV, and θ is a vector of length m_Z linking the covariate vector Z_i to the risk of transmission in utero or during delivery for those infants who are infected before time t_c. These two regressions reflect the different mechanisms that govern whether a mother ever transmits HIV to her child and whether that child was infected before birth. Using this formulation, we can include covariates as appropriate based on their known associations with modes of MTCT of HIV. For example, an intervention that happens to the child after birth, independent of HIV status at birth, could inform θ and not η.

Equations 5 and 6 link covariates to the mode of transmission but do not allow the covariates to inform timing of breastfeeding transmission. We link these predictors Z_i to the time to breast milk infection through a proportional hazards model in which we define the ith infant's hazard at time u as

$$h(u|Z_i)=h_0(u)\exp(Z_i'\beta),$$

where $h_0(u)$ describes the baseline hazard function and β is a parameter vector linking Z_i. When specifying $h_0(u)$, we could either use a parametric model, such as the Weibull distribution ($h_0(u) = u^\gamma$), or a semi-parametric model, specifying the hazard as piecewise-constant, for example. Often, because, hazard rates for MTCT after 4–6 weeks have been observed to be constant over time (The Breastfeeding and HIV International Transmission

Study Group, 2004), an exponential distribution is used to model the timing of MTCT via breastmilk. However, the risk of transmission may be higher at the start of breastfeeding; therefore, we will assume a Weibull distribution which we believe has an adequately flexible baseline hazard.

2.3 Likelihood

The likelihood for the *i*th infant is the product of Equations 2 and 4. The full data likelihood, assuming the test times are independent of the test results and the infection time conditional on the model, is then

$$L(\beta,\gamma,\omega,\eta,\theta,\pi)=\prod_{i=1}^{N}\{p(Y_{i1},\ldots,Y_{im_i}|s_i,t_i,\omega,\pi)f(s_i|\beta,\gamma,\theta,\eta)\}. \tag{7}$$

2.4 Priors and posterior

Now that we have specified the likelihood, we turn our attention to prior specification. We specify the following distributions as priors for (β, θ, η, ω, τ_0, γ, π):

$$\beta \sim N_{m_Z}(b_1,b_2),\quad \theta \sim N_{m_Z}(t_1,t_2),\quad \eta \sim N_{m_Z}(e_1,e_2)\quad \omega \sim N_3(o_1,o_2),$$
$$\log(\tau_0) \sim N(o_3,o_4),\ \ \gamma \sim \text{Gamma}(g_1,g_2)\ \text{and}\ \pi \sim \text{Beta}(o_3,o_4),$$

where $N_n(a; b)$ is the multvariate normal distribution with mean vector a of length n and $n \times n$ covariance matrix b, $N(a, b)$ is the univariate normal distribution with mean a and variance b, Gamma(a, b) is the gamma distribution with shape parameter a and scale parameter b and Beta(a,b) is the beta distribution with parameters a and b. While we will specify most parameters to be non-informative, we will use information from previous studies to inform the distributions of ω and π. The question of sensitivity and specificity of HIV RNA and DNA PCR tests in infants born to HIV infected moms has been adressed in the literature in non-breastfeeding populations. We will use this information to set the parameters of the prior distributions of $\omega_0, \ldots, \omega_p$ in Section 3.

2.5 Estimation

We use the Gibbs sampler (Gelfand and Smith, 1990) to sample from the posterior distribution of the parameters. Because the parameters in the model do not have conjugate prior distributions, their full conditional distributions are not analytically available. Therefore, we used the slice sampler (Neal, 2003) for constrained parameters and shortcut metropolis (Neal, 2005) for unconstrained parameters to obtain samples from their full conditionals. Sampling s_i presented a particular challenge due to its discontinuous distribution. Details are given in Web Appendix 1. The estimation procedure was implemented in R (R Development Core Team, 2006) and C and is available as an R package from the author. The code has been validated through simulations (see Web Appendix 2).

3. Analysis of HPTN 024

The HIV Prevention Trials Network (HPTN) 024 study was a multisite, placebo-controlled, double blinded randomized trial of antibiotics to prevent perinatal MTCT of HIV-1 conducted in Tanzania, Malawi and Zambia (Taha et al., 2006). HIV-1 infected pregnant women were enrolled at 20–24 weeks gestation and followed until delivery. Their liveborn infants were followed with HIV testing initially scheduled to be for birth, 4–6 weeks and 3,

6, 9 and 12 months. The 3 month test was dropped shortly after commencement of the study. The majority of 4–6 week visits occurred between 6 and 8 weeks. According to protocol, samples collected at 3, 6 and 9 months were only tested if the 12 month sample was positive or missing. The 12 month sample was only to be tested if an antibody test at 12 months was positive. The protocol specified that HIV-1 RNA be detected with the BioMerieux NucliSens HIV-1 QL assay for the Malawi and Zambia sites and with the Roche HIV-1 Amplicor Monitor assay version 1.5 for the Tanzania site in a reference laboratory (University of North Carolina, Chapel Hill, North Carolina, USA); however, due to logistical constraints, some infant dried blood splots from Malawi and Zambia were tested using the Roche assay. For confirmation of the infant's HIV-1 infection a second sample (from a subsequent protocol scheduled visit) was tested whenever possible. Of primary scientific interest was the comparison of the sensitivity of these two assays.

The analysis included 1977 infants who had at least one HIV test. One hundred and eighteen infants who tested positive when they were less than 24 hours old were assigned $s_i = 0$. Six hundred and eighty six infants who had a negative antibody test at 12 months were assigned $s_i = \infty$. All other infants had s_i unknown and therefore sampled as part of the MCMC algorithm.

Several variables were included as predictors of timing of MTCT based on those factors shown to be information of timing of detection of HIV infection in infants in the literature. These variables along with the parameters corresponding to the regressions in which they were included in were: maternal CD4 count (θ, η), viral load (all), hemoglobin (all) and weight (all) measured at enrollment; maternal cervical viral load at delivery (all); indicators of infant (θ) and mother nevirapine (θ, η) dosing; randomization arm (θ, η); sex of the infant (all); infant birth weight (η); mode of delivery (θ, η); duration of ruptured membranes (θ, η); indicator of early infant death (θ, η); an indicator of breastfeeding for longer than 6 months (θ, η) and site (θ, β). These variables were not selected to build a model to address hypotheses of scientific interest, but instead to obtain the best possible estimate of the timing of infection, s_i and thus parameter estimates should be interpreted with caution. Infants born to HIV-1-infected mothers are only at risk for MTCT of HIV while breastfeeding. At one site (Tanzania), mothers were counseled to stop breastfeeding by the time their infants reached 6 months of age, and, by 6 months of age, over 90% of the the infants at this site had been weaned. In contrast, over 90% of the infants at the 3 remaining sites were still breastfeeding at six months.

Sensitivity was modeled according to Equation (1) with $p = 2$ and x_1 indicating the ith infant's assay type at time t_{ij}. Information is available from several studies about the sensitivity of PCR tests in infants infected in utero or during delivery and is summarized graphically in Figure 1. These data were used to construct mildly informative priors for sensitivity, where $\omega_0 \sim N(-1, 0.06)$, $\omega_1 \sim N(0, 0.05)$, $\omega_2 \sim N(0, 25)$ and $\log(\tau_0) \sim N(0, 0.06)$. Lines representing sensitivity over time for $s_i = 0$ based on 1,000 random draws from the prior distribution are also plotted on Figure 1. The priors on ω_1 and τ_0 suggest that the change in sensitivity over time does not depend on the mode of transmision. The prior for π =1-specificity was set as beta(1; 1000) to reflect the belief that false positives are rare.

Priors for the distribution of the timing of MTCT were also based on historical data. With mother and infant exposed to a single dose of nevirapine, the rate of in utero/devliery transmission (not adjusted for sensitivity and therefore possibly underestimated) has been estimated to be between 0.05 and 0.10 (Thistle et al., 2007; Taha et al., 2004; Guay et al., 1999). Cumulative rates of transmission into the late postnatal period for three independent studies are shown in Figure 2. This plot also summarizes the prior distribution for timing of MTCT of HIV (specified as $\gamma \sim$ gamma(4.2, 10), $\beta_0 \sim N(-3.4, 4)$, $\beta_j \sim N(0, 4)$, $j = 1, \ldots, 10$,

$\eta_0 \sim N(-0.4, 0.25)$, $\eta_j \sim N(0, 25)$, $j = 1, \ldots, 13$, $\theta_0 \sim N(-1.1, 1)$ $\theta_j \sim N(0, 25)$, $j = 1, \ldots, 17$). The percentiles of the distribution were calculated by simulation. The results from the previous trials were all contained within the interquartile range of the prior distribution. Additionally, the interval defined by the 2.5th and 97.5th percentiles represents a plausible range of possible outcomes (although the upper end may be higher than expected). The three studies shown also reflect a range of breastfeeding behaviors with 30–80% still breastfeeding at 12 months. Because we are modeling transmission risk conditional on breastfeeding throughout the follow-up period, we might expect our estimates to be closer to the higher estimates shown in Figure 2. The parameters for the distributions were obtained using nonlinear least squares treating each time point from each study as a separate observation.

We ran the Gibbs sampler twice for 100,000 iterations each based on different starting values for the parameters and seeds for the random number generator. Figure 3 shows density estimates from the posterior draws of the parameters that determine the time-varying sensitivity, ω and τ_0. The densities of the prior distributions are shown with the density estimates of the marginal posteriors distributions. These do not indicate that the results were driven by the prior distributions on these parameters. Table 1 lists the posterior means, standard deviations, medians and highest posterior density intervals for for ω and τ_0. Estimates for the coefficient in the transmission time models are shown in Web Appendix 3. The MCMC chains appeared to mix well.

The main parameter of interest was the difference in sensitivity between the two assays, ω_2, which had a posterior mean and median equal to −0.19 with a 95% HPD interval equal to (−0.45, 0.09). Although the point estimate was less than 0 suggesting that the Roche assay may be less sensitive, there was no statistically significant association. Likewise there was no statistical difference between the mean ages at detection of in utero/delivery infections or the mean times from transmission to detection for the two assays. The estimate of ω_1 suggests that the sensitivity curve for breastfeeding transmission increases more slowly than the curve for in utero/delivery transmission. Figure 4 plots the posterior estimates and 95% credible intervals of sensitivity over time for infants infected in utero/during delivery and infants infected via breastmilk. At six weeks of age, we would expect to detect between 97 and 98% of in utero/delivery transmission. Based on the estimate of τ_0, this corresponds to approximately an average of 8 weeks after transmission. The sensitivity for detecting an infection 8 weeks after breastfeeding transmission was 72–78%.

Figure 5 plots the cumulative proportion of infected and positive infants over time. The solid black line represents the posterior mean of cumulative distribution of s_i from the model and represents the cumulative proportion of infants who are infected. The dashed and dotted lines represent the cumulative distribution of detection times, the times we would expect to first be able to detect infection, for the two assays. The grey line represents the estimate of the cumulative distribution based on Kaplan-Meier. The event time here was taken to be the midpoint between the last negative test and the first positive test. As expected, accounting for the imperfect sensitivity suggests that the estimated proportion of infected infants at any time is smaller than the truth, but the distance between the estimates decreases with time. This decrease is expected because the rate of new infections decreases over time. The Kaplan-Meier estimates may also be lower than the model-based estimates due to the lag in testing time (i.e., the infants are not tested as soon as infection is detectable).

Additional analyses were performed considering alternative prior distributions and are summarized in Web Appendix 3. While investigating alternative prior distributions, it became apparent that for this data set mildly informative priors were necessary to prevent the MCMC sampler from getting stuck in a degenerate state. However, this may be unique

to the data set under consideration as similar problems did not occur under extensive simulations (Web Appendix 2). Given the priors were based on mulitple historic studies and are quite liberal in values they allow for sensitivity and the survival distribution (Figures 1 and 2), we do not see the need for well-informed priors as a drawback in the current study. It is important however, to interpret the results in the context of the prior distributions.

4. Discussion

We present a method for estimating the time-varying sensitivity of a diagnostic assay when the gold standard is only observed on a subset of the population. Although this model was tailored to assays for mother-to-child transmission of HIV, the underlying ideas are generally applicable in any setting where a diagnostic test with time-varying sensitivity is given repeatedly over time to detect incident disease.

This model is novel in several aspects. It is the first Bayesian approach to estimating time-varying sensitivity in this setting and allows incorporation of historical data. Although similar to Gupte et al. (2007)'s maximum likelihood approach to estimating the time-varying sensitivity and specificity of HIV-1 viral assays for detecting MTCT, our approach differs in several important ways. First we do not group the testing times around the visit times. Second, we do not force the sensitivity to be 0 at birth. Third, we allow for a more flexible event time distribution (Weibull versus exponential), and, fourth, we include information from previous studies about the sensitivity of these assays. This possibly gave us precision that Gupte et al's study lacked. Their estimate for the mean time from transmission to detection for breastfed infants was 12.7 days with a standard error of 276.5 days. While our estimate was larger at 34 days, our standard error was lower at 11 days. Note additionally, that our 95% credible interval (15, 55 days) is contained entirely within their 95% confidence interval (−530, 556 days). Their shorter estimate of the mean time between infection and detection for breastfeeders may also be a side effect of forcing the in utero/delivery sensitivity curve to equal 0 at birth. This in turn may have forced negatives at birth who were then positive at 10 days to be classified as breastfeeding transmissions which in turn would force the slope of the breastfeeding transmission sensitivity curve to be higher than it may actually be. A strength of their study was the additional visit for HIV testing at 10 days after birth. Additional advantages of Gupte et al's approach are that it is more computationally straight-forward to implement and, because of the discretized time scale, potentially more straight-forward for model checking.

As with any modeling strategy, the one we present is not without potential drawbacks. In building the model, we assume that the test results are independent conditional on the true timing of infection, s_i, and the model for time-varying sensitivity. For the data set in question, we believe this to be a reasonable assumption because of the spacing of the visits that were on average 12.2 weeks apart (median = 6.3 weeks). This implies that the sensitivity profile would rise quickly enough so that by the time of a second test after infection, sensitivity would be 100%. While this may be true on average, there may be some infants for whom this assumption is too strong. For example, if two positive tests occur close together and the infant's circulating virus levels are rising much faster than average in the population, assuming the population curve for the individual may force the estimate of s_i to be smaller than the true s_i. In such cases, estimation of s_i may be negatively impacted which then may impact estimation in the overall model. In limited simulations assuming the sensitivity profile estimated from the HPTN 024 data, we found that the higher the correlation between the tests, the larger the bias in the results in the direction of underestimating the mean time to first positive test (Web Appendix 2), suggesting that the expected time between infection a first positive for HIV infected infants may be even longer than estimated here. The magnitude of the bias at varying levels of dependence was

comparable to the independence assumption until the extreme case where the probability of testing positive at any time point after a positive test was one. Still the 95% credible intervals contained the true value. Building models that appropriately model the conditional independence is challenging. Some of the potential difficulties include specifying the correct form of dependence between the assays at different time points, especially when the assays change over time as in this study. Additionally, the timing of the tests was assumed to be independent of the test results. If instead the testing schedule is dependent on test results, this would need to be accounted for in the likelihood. This approach also relies on parametric assumptions for the time to transmission distribution and the sensitivity profile. These parametric assumptions may not in fact be valid and so the results should be interpreted with that caution in mind.

The research presented here adds to scientific knowledge in many ways. First, we present a model for estimating the time-varying sensitivity of a diagnostic assay and comparing the profiles of several assays when there is not a fully observed gold standard and disease status changes over time. This model can incorporate covariate information both about the disease and the sensitivity. Second, we show how historical data can be incorporated into priors to inform estimates about sensitivity and specificity. Last, we present new data about the time-varying sensitivity in infants born to HIV-infected mothers of two widely used HIV-1 diagnostic assays. Finally, this model can also be used to make inference about timing of infection either through inclusion of covariates of interest or through imputation procedures using the samples of the individual transmission times.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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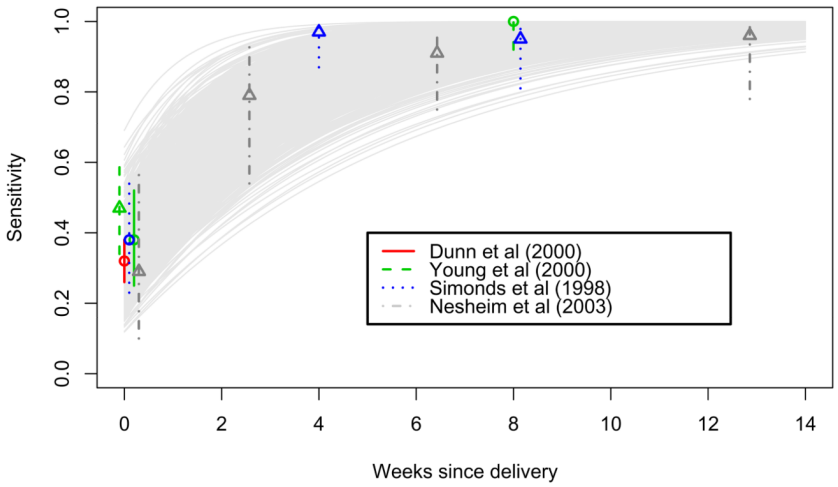

Figure 1.
The circles represent sensitivity estimates for DNA PCRs from previous studies with 95% CIs (vertical bars). The triangles represent sensitivity estimates for RNA PCRs from previous studies with 95% CIs (vertical bars). The gray lines represent 1,000 random draws of the sensitivity curve for in utero/delivery transmission from the prior distribution of ω_0, …, ω_p and τ_0.

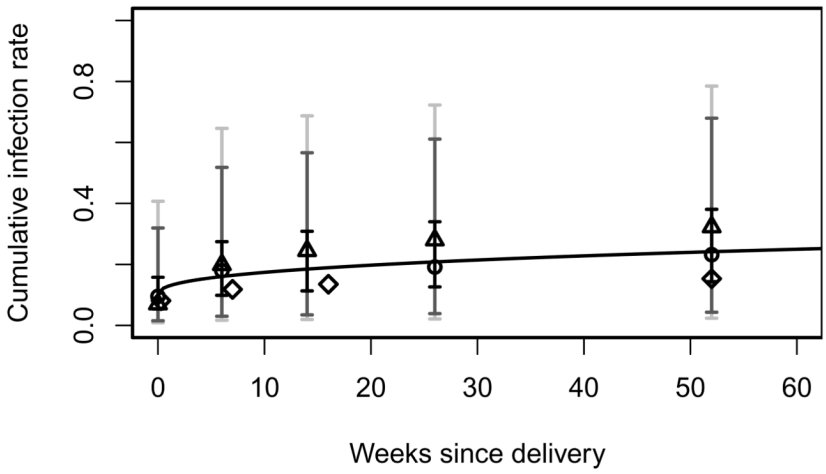

Figure 2.
Graphical depiction of prior on time to HIV transmission. The solid black curve represents the mean over time. The vertical bars represent pointwise 50% (black) and 95% (gray) intervals. Information from historical data is also included: circles=Taha et al. (2007), triangles= Nduati et al. (2000, breastfeeding arm), diamonds=Jackson et al. (2003).

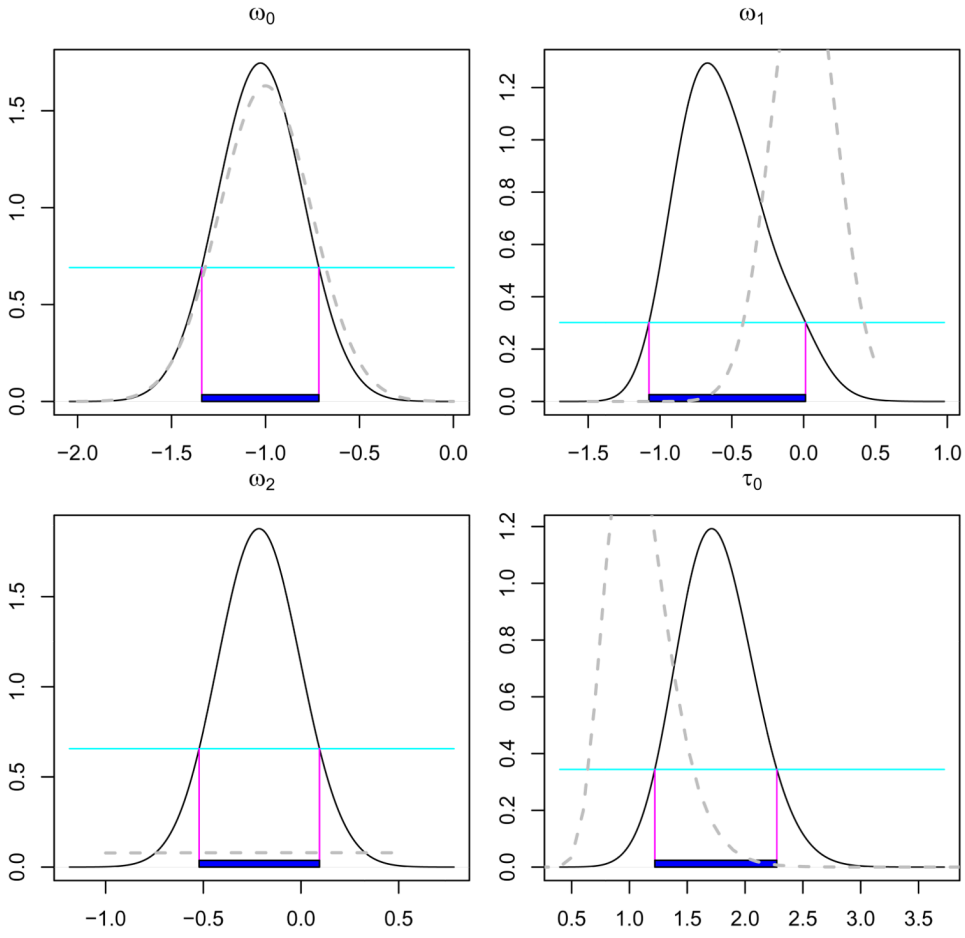

Figure 3.
Summaries of samples from the posterior distribution of the parameters describing sensitivity over time. The thick horizontal line with vertical bars at the end on the density plots represents the HPD interval. The dotted gray line indicates the prior distribution. A horizontal gray line represents the value of the density at the ends of the interval. The chains appeared to mix well.

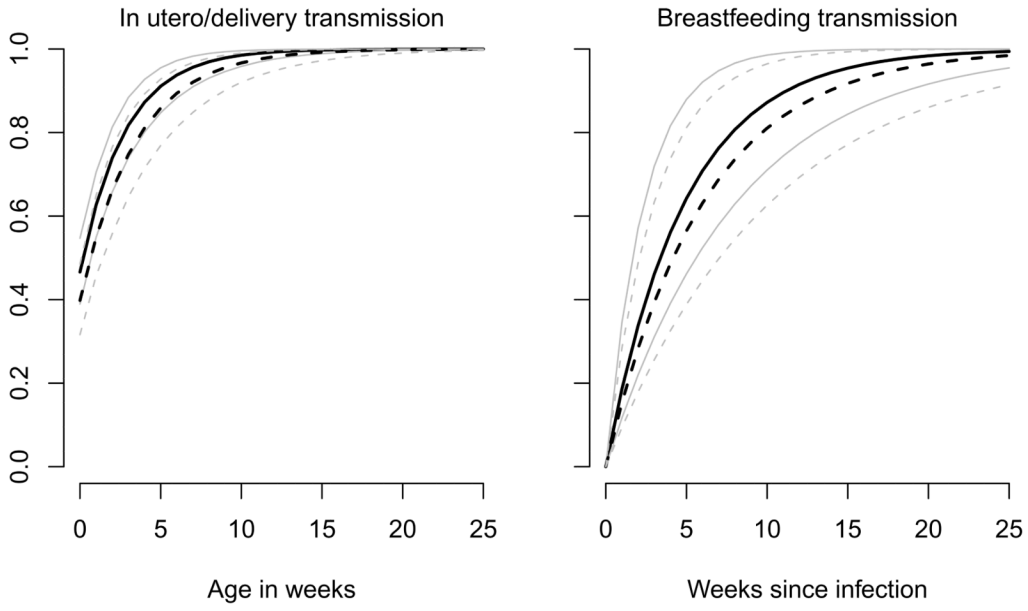

Figure 4.
Posterior estimates of sensitivity over time for in utero/delivery transmission and breastfeeding transmission. 95% credible intervals are shown in grey. Solid line = BioMerieux NucliSens HIV-1 QL assay. Dashed line=Roche HIV-1 Amplicor Monitor assay.

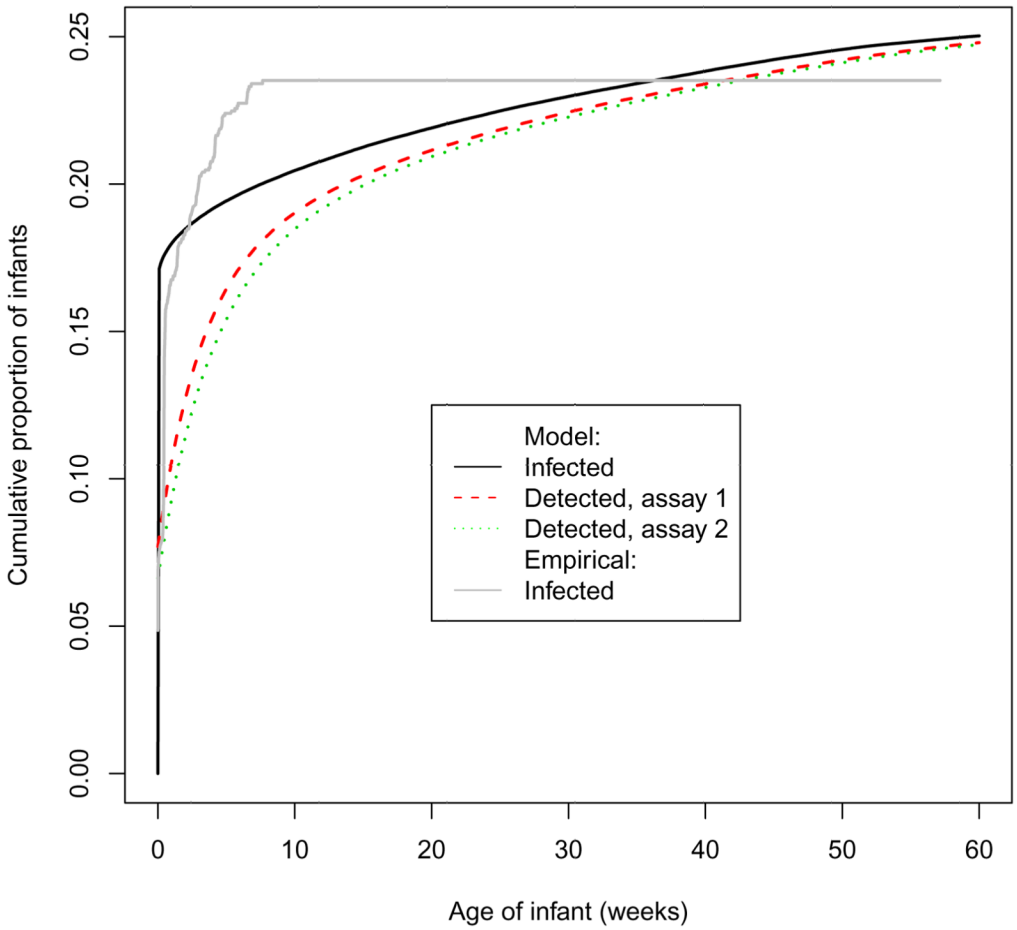

Figure 5.
Posterior estimates of the cumulative proportion of HIV infected infants, detected infections by assay (1= BioMerieux NucliSens HIV-1 QL; 2= Roche HIV-1 Amplicor Monitor), and infected infants based on unadjusted Kaplan-Meier estimates.

Table 1

Posterior summaries of sensitivity parameters

Parameter	Median	Mean	st. dev.	95%HPD interval
ω_0	−1.15	−1.15	0.14	(−1.41, −0.86)
ω_1	−0.73	−0.71	0.23	(−1.13, −0.25)
ω_2	−0.19	−0.19	0.14	(−0.45, 0.09)
τ_0	1.85	1.87	0.28	(1.33, 2.44)
Mean age at detection (weeks), in utero/delivery transmission				
BioMerieux NucliSens HIV-1 QL assay	1.05	1.07	0.34	(0.43, 1.73)
Roche HIV-1 Amplicor Monitor assay	1.70	1.73	0.52	(0.76, 2.77)
Mean time from breastfeeding transmission to detection (weeks)				
BioMerieux NucliSens HIV-1 QL assay	5.21	5.13	1.63	(2.14, 8.00)
Roche HIV-1 Amplicor Monitor assay	6.23	6.29	1.97	(2.71, 10.1)