Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening

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Background: Surveillance programmes for prevention of mother-to-child transmission of HIV (PMTCT) fail to quantify numbers of infant HIV infections averted, often because of poor postnatal follow-up. Additionally, infected infants are often not identified early and only gain access to comprehensive HIV care and treatment late in their disease.

Methods: Anonymous, unlinked, HIV prevalence testing was conducted on dried blood spot (DBS) samples from all infants attending 6 week immunization clinics at seven primary health care clinics offering PMTCT. Samples were tested for HIV antibodies (indicating maternal HIV infection) and those determined to be from HIV-exposed infants were tested for HIV RNA by polymerase chain reaction. Infant and child mortality rates were determined using birth histories.

Results: Samples were collected from 2489 infants aged 4–8 weeks. HIV antibodies were identified in 931 infants [37.4%; 95% confidence interval (CI), 35.4–39.4], of whom 188 were HIV RNA positive. The estimated vertical transmission rate (VTR) was 20.2% (95% CI, 17.8–23.1%); 7.5% of all infants at this age were infected. Amongst mothers who reported that they had taken single-dose nevirapine for PMTCT, VTR was 15.0%. Amongst women who reported being HIV uninfected but whose infants had HIV antibodies, VTR was 30.5%. Infant mortality rates in KwaZulu Natal increased from 28/1000 live births in 1990–1994 to 92/1000 in 2000–2004.

Conclusions: Anonymous HIV prevalence screening of all infants at immunization clinics is feasible to monitor the impact of PMTCT programmes on peripartum infection; linked screening could identify infected children early for referral into care and treatment programmes.

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Introduction

In spite of substantial financial and human resource investments in prevention of mother-to-child transmission of HIV (PMTCT), it remains unclear to what extent these programmes have reduced the number of children becoming infected or dying with HIV each year. Large numbers of infected children continue to present to public health facilities, often with advanced disease. Peripartum transmission can be significantly reduced by effective delivery of zidovudine from about 36 weeks or by single-dose nevirapine (NVP) to mother and exposed infant at the time of delivery [1,2]. However, UNAIDS estimate that only about 10% of HIV-infected pregnant women globally receive prophylaxis to prevent HIV transmission [3].

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HIV/AIDS accounts for more than 20% of child deaths in southern Africa compared with approximately 3% globally [4]. In South Africa, conservative estimates suggest that infant mortality rates increased from 48/1000 liveborn infants in 1990 to 60/1000 in 2000 [5] and HIV accounts for at least 40% of deaths in children under 5 years of age [6].

Efforts to monitor and evaluate PMTCT initiatives have generally focused on individual components and process indicators such as acceptance rates for counselling and/or testing [7–9]. The present study analysed dried blood spots (DBS) collected anonymously from 6-week-old infants attending immunization clinics in KwaZulu Natal. HIV prevalence in these infants reflects the cumulative effectiveness of PMTCT interventions on peripartum transmission including the identification HIV-infected women and provision of PMTCT prophylaxis. This was combined with a simple birth history to determine infant and child mortality as an indirect indicator of the effects of HIV and the effectiveness of interventions to reduce opportunistic infections.

Methods

Routine anonymous, unlinked, HIV prevalence testing was conducted on infants attending immunization clinics at 6 weeks of age in three periurban and four rural clinics in KwaZulu Natal. Surveillance information was collected by local community health worker volunteers employed and specifically trained for the project. Single-dose NVP was routinely offered to HIV-infected mothers at the time of labour and to their infants within the first 48 h of life. Following explanation of unlinked testing for HIV, mothers were asked for written informed consent. Blood samples were collected onto filter paper and dried before testing for HIV antibodies (maternal) using a commercial enzyme-linked immunosorbant assay (Vironstika HIV-1 IMPVD, Organon Teknika/Biomerieux, Durham, North Carolina, USA). If antibodies were detected, indicating HIV exposure of the infants, the samples were then tested using a qualitative HIV RNA molecular assay (Organon Teknika quantitative RNA assay) to establish HIV infection status. Basic demographic data as well as mothers' experiences of HIV testing and receipt of NVP during her pregnancy were also recorded. Mothers were all offered linked polymerase chain reaction (PCR) testing for HIV for their infants with immediate results.

All mothers of children attending for any immunization were asked about the outcome of previous pregnancies to estimate infant and child mortality rates over the previous 15–20 years.

The study was commissioned by the KwaZulu Natal Provincial PMTCT programme and approved by the Biomedical Research Ethics Committee of the Nelson R. Mandela School of Medicine (E076/04, 10 June 2004).

Statistical analysis

Maternal and infant HIV prevalence rates amongst the total number tested were derived from the prevalence of antibodies and HIV RNA, respectively; the vertical transmission rate is the number of infants infected amongst the infants born to HIV-infected mothers. Second twins were excluded from all analyses as they could not be considered as independent observations. Factors associated with transmission or NVP uptake were investigated in univariable and multivariable regression analyses following a backwards stepwise approach including variables in the model; the variance inflation factors were monitored and colinearity assessed. For the transmission analysis, all mother–child pairs with a positive antibody test result and available RNA PCR test result were included and the PCR result was taken as the outcome variable. NVP uptake analysis was also restricted to antibody-positive pairs, and the outcome variable was the mother's self-reported swallowing of the NVP tablet. Variables thought to be of interest or to have potential influence were included in the models irrespective of significance. The multivariable transmission analysis was adjusted for age at sampling to account for postnatal transmission.

Mortality rates were calculated based on previous children of the mothers in the sample. The current child was excluded from the analysis as they had to be alive at the time of interview, but all previous children were considered and mortality reported by the mother was taken as the end point. The infant mortality rate was calculated as the number of deaths per 1000 children < 12 months old out of the total number of livebirths 12 months or more before the interview. The child mortality rate was calculated as the number of deaths per 1000 children < 5 years old out of the total number of livebirths more than 5 years before the interview. The survival analysis was conducted using a Cox proportional hazard model [10].

Results

Between August 2004 and July 2005, 11 140 caregivers of infants brought to the clinics for immunization were approached for interviews (9334 mothers, 144 fathers, 632 grandmothers, 830 other household members and 200 non-household members). Of these, 2856 were mothers of 2927 infants 6 weeks of age from whom consent to collect DBS was requested (Fig. 1). The majority of mothers consented (2501; 87.5% uptake rate) resulting in 2585 infants with samples. Results of 96 infants were excluded from the analyses either because they were a second twin or the PCR result was missing, leaving 2489 infants in the transmission analyses. Amongst all

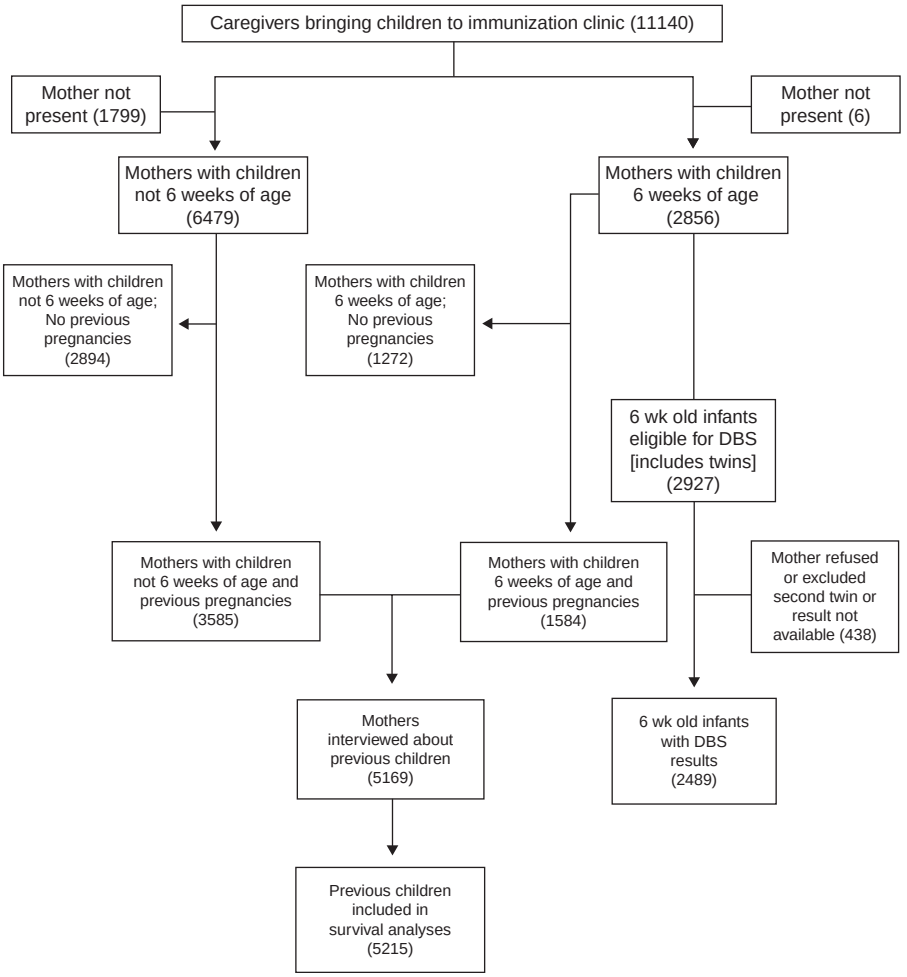

Fig. 1. Infants analysed in the survey between August 2004 and July 2005. DBS, dried blood sample.

interviewees 5169 women had more than one child and could, therefore, provide data for the mortality analysis. The characteristics of the women interviewed and permitting DBS samples from their infants are detailed in Table 1.

Maternal prevalence

HIV antibodies, indicating HIV exposure, were detected in 931 infants [37.4%; 95% confidence interval (CI), 35.5–39.4). These maternal prevalence rates varied with maternal age; the prevalence was 20.8% (95% CI, 17.7–24.2) in mothers aged 16–20 years, which was significantly lower than that in women aged 20–29 years (45.5%; 95% CI, 42.7–48.3) ($P < 0.001$) or women more than 30 years (38.0%; 95% CI, 33.9–42.2); the higher prevalence in 20–29 year old women compared with women >30 years was also statistically significant ($P = 0.003$).

Infection rates in infants at 4–8 weeks of age

Overall, 188 infants were infected, giving a vertical transmission rate of 20.2% (95% CI, 17.8–23.1) amongst the 931 exposed infants and equating to a 7.5% (95% CI, 6.5–8.6) HIV prevalence rate amongst all infants tested. Reported NVP usage was associated with reduced transmission: 15% (95% CI, 11.9–18.6) in NVP exposed compared with 26.0% (95% CI, 21.9–30.3) in mothers who did not report having taken NVP. The transmission rate among women who reported themselves as HIV infected was 15.6% (95% CI, 12.5–19.1); among mothers who reported themselves as HIV uninfected but whose infants were antibody positive the transmission rate was 30.5% (95% CI, 24.0–37.6). Women who did not report their status had an intermediate risk of transmission (22.3%; 95% CI, 17.1–28.2).

Reported NVP use was significantly associated with lower transmission rates in univariable analysis compared with when NVP was not reportedly used [odds ratio (OR), 0.50; 95% CI, 0.36–0.70; $P < 0.001$]. Home delivery was associated with twice the transmission risk compared with clinic delivery (OR, 1.97; 1.04–3.71; $P = 0.037$) but the difference between home and hospital delivery was not significant (OR, 0.86; 95% CI, 0.57–1.29; $P = 0.466$). HIV-infected women who attended antenatal clinic on more than three

Table 1. Characteristics of mothers interviewed at immunization clinics[a] and mothers who consented to a dried blood sample being taken from their infant[b].

Variable	Immunization clinic	DBS
Total No. interviewed and included in the analysis/total No. consenting for infant DBS	5169	2501
Total No. children included in mortality analyses/DBS results reported	5215	2489
Median age of mother [years (IQR)]	32 (27–37)	24 (20–30)
Mother lives with baby's father [No. (%)]	2095 (42)	710 (28)
Mother lives with her mother [No. (%)]	2497 (50)	1552 (62)
Mother lives with relatives [No. (%)]	3066 (62)	1641 (66)
Mother lives with non-relatives [No. (%)]	189 (4)	122 (5)
Self-reported infected [No. (%)]	1059 (21)	544 (22)
Income to spend on themselves [No. (%)]	2477 (50)	803 (33)
Plan to leave area in next 3 months [No. (%)]	317 (6)	168 (7)
Arrived in area in last 6 months [No. (%)]	313 (6)	154 (6)
Median age at DBS [days (IQR)]		45 (42–49)
Breastfed previous child (DBS from current child) [No. (%)]	2066 (76)	809 (73)
Formula fed previous child (DBS from current child) [No. (%)]	319 (12)	157 (14)
Fed previous child both milk types (DBS, current child) [No. (%)]	215 (8)	138 (12)

DBS, dried blood spot sample.
[a]Immunization column includes all women who were interviewed and for whom this was not the first child and, therefore, had data that could be included in the mortality analysis.
[b]A child could not be in both the immunization clinic and DBS column; DBS only applied to current children and the immunization clinic column excludes these. However, mothers with several children could have been in both groups.

occasions were less likely to transmit the virus (OR, 0.67; 95% CI, 0.43–1.02), although this effect was of borderline significance univariably ($P = 0.064$) and further reduced after adjustment for other covariates. In multivariable analysis, the odds changed little, and reported non-use of NVP and home deliveries remained significantly associated with increased MTCT risk.

Factors associated with nevirapine use in HIV-infected mothers

In univariable analyses, possession of a PMTCT White Card (a patient-held medical record that indicates enrolment in the provincial PMTCT programme) and self-report of HIV infection were strongly associated with reported NVP use (Table 2). The mothers' living arrangements significantly influenced whether she used NVP, whereas mothers' age, parity, infant feeding preference, antenatal attendance pattern and recent arrival in the community did not (Table 2).

Of the women who self-reported being infected, 93% also reported taking NVP, with only one woman whose infant was negative for HIV antibodies reporting taking NVP. However, in addition to these

Table 2. Univariable and multivariable analysis of variables associated with reported nevirapine uptake (based on 434 mothers of infants with positive HIV antibody results on dried blood samples).

Variable	No.	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
PMTCT White card (ref: no card available)	85	10.63 (5.56–20.34)	0.000	1.72 (0.41–7.19)	0.455
Family (ref: mother living alone)					
Mother and infant living with infant's father only	75	1.01 (0.38–2.73)	0.979	74.88 (4.40–1273.3)	0.003
Mother and infant living with other people, father not present	263	1.09 (0.43–2.72)	0.853	8.40 (1.65–42.61)	0.010
Mother and infant living with other people, father present	61	0.97 (0.35–2.68)	0.954	9.58 (0.94–97.72)	0.056
Mother not living with infant	15	0.81 (0.21–3.17)	0.767	2.58 (0.17–38.82)	0.494
Mother arrived in community in last 6 months (ref: present for > 6 months)	36	0.93 (0.47–1.85)	0.837	1.91 (0.15–23.88)	0.616
Attended antenatal clinic > 3 times (ref: ≤ 3)	373	1.49 (0.86–2.60)	0.164	1.16 (0.19–7.28)	0.870
Number of pregnancies (ref: 1)	434	1.15 (0.98–1.34)	0.086	1.43 (0.78–2.62)	0.246
Year of birth of mother (ref: < 1975)					
1975–1984	267	0.74 (0.47–1.16)	0.191	2.06 (0.48–8.89)	0.334
1985–1994	59	0.53 (0.28–1.02)	0.057	1.73 (0.15–19.36)	0.657
Milk type given to this child (ref: breast)					
Formula	102	2.41 (1.52–3.83)	0.000	0.77 (0.22–2.72)	0.683
Both	28	0.93 (0.42–2.05)	0.850	2.29 (0.15–34.97)	0.552
Report HIV status (ref: uninfected)					
Infected	211	1705 (220–13 212)	0.000	5237.92 (394–69 641)	0.0001
Not reported	110	1.03 (0.06–16.6)	0.985	0.98 (0.06–16.74)	0.988

Percentages calculated using total number of available data as the respective denominator. PMTCT, prevention of mother-to-child transmission of HIV; OR, odds ratio; CI, confidence interval.

women, there were also 172 (6.9% of the total) who reported themselves as uninfected but whose infants were found to be antibody positive, with only two of these women reporting use of NVP. There were 37 women (1.9% of the total) who reported themselves as infected but whose infants were found to be antibody negative, suggesting either a false negative in the infant DBS testing, a false-positive maternal antenatal test or a misunderstanding of the post-test counselling; of these women 76% had taken NVP.

Mortality

Infant mortality in KwaZulu Natal trebled since 1990 from 28.4/1000 livebirths in infants born in 1990–1994 to 91.5/1000 amongst infants born in 2000–2005 (Table 3). Child mortality followed a similar pattern. In univariable analysis, factors associated with mortality included mothers self-reported infection status, one or more dead sibling, maternal age, maternal income, and infant gender. In the multivariable analysis, the increased mortality in children born to the youngest mothers was no longer significant.

Discussion

Over 7% of all 6-week-old infants attending immunization clinics in the study and 20% of those born to mothers with HIV infection were themselves HIV infected. Attendance rates at immunization clinics in KwaZulu Natal are generally high, especially for the first diphtheria/tetanus/pertussus immunization at 6 weeks of age [11]; we assumed that the study population closely represents all infants regardless whether their mothers accepted antenatal PMTCT interventions including HIV testing and NVP, whether they delivered at a health facility or at home, and whether they were HIV infected or uninfected at first antenatal booking and infected later in pregnancy. If all HIV-infected women had been identified and they and their infants had received NVP for PMTCT then a transmission rate of approximately 12% would have been expected [12]. Instead we estimated a transmission rate of 20% overall, and 15% in those who reported NVP use; in this way the surveillance approach demonstrates the cumulative effectiveness of PMTCT interventions to reduce peripartum transmission and the

Table 3. Infant and child mortality rates and univariate and multivariate Cox regression analysis.

		Mortality rate (per 1000 livebirths)		Hazard ratio[b]			
Variable	No.[a]	Infant	Child	Unadjusted (95% CI)	*P* value	Adjusted (95% CI)	*P* value
Child date of birth							
2000–5	1430	91.5 (76.7–108.1)	–				
1995–9	1813	49.0 (39.5–59.9)	67.7 (56.6–80.5)	0.537 (0.423–0.682)	0.000	0.597 (0.465–0.766)	0.0001
1990–4	1196	28.4 (19.7–39.5)	40.1 (29.7–52.8)	0.344 (0.252–0.469)	0.000	0.404 (0.290–0.564)	0.0001
<1990	776	51.5 (37.1–69.5)	73.5 (56.1–94.1)	0.584 (0.432–0.790)	0.000	0.740 (0.524–1.04)	0.087
Maternal HIV status							
Negative	2727	51.3 (43.3–60.3)	57.7 (47.8–68.9)				
Positive	965	79.7 (63.4–98.7)	64.1 (46.8–85.4)	1.447 (1.131–1.851)	0.003	1.322 (1.027–1.701)	0.030
No comment	17	58.8 (1.5–286.9)	–	0.916 (0.128–6.539)	0.931	0.637 (0.088–4.592)	0.654
Missing	1506	48.5 (38.1–60.7)	61.1 (47.7–77.0)	1.109 (0.880–1.397)	0.379	1.105 (0.874–1.398)	0.404
Child sex							
Female	2582	47.9 (40.0–57.0)	51.3 (41.7–62.2)				
Male	2633	63.5 (54.4–73.5)	68.2 (57.2–80.6)	1.192 (0.979–1.450)	0.080	1.178 (0.967–1.435)	0.104
Mother arrived in community in last 6 months							
No	4885	56.0 (49.7–62.9)	58.7 (51.2–67.0)				
Yes	330	52.1 (30.7–82.2)	75.2 (44.4–117.7)	1.173 (0.804–1.712)	0.408	1.072 (0.728–1.577)	0.725
Disposable income							
No	2395	60.8 (51.5–71.2)	60.6 (49.6–73.2)				
Yes	2820	51.6 (43.7–60.4)	59.0 (49.3–70.0)	0.846 (0.691–1.029)	0.095	0.891 (0.728–1.090)	0.262
Mothers year of birth							
<1965	624	45.1 (30.2–64.5)	49.7 (33.3–71.1)				
1965–74	2677	49.3 (41.4–58.2)	59.0 (49.5–69.7)	1.269 (0.890–1.809)	0.189	1.364 (0.947–1.964)	0.095
1975–84	1839	65.4 (54.4–77.8)	67.7 (52.8–85.2)	1.779 (1.240–2.553)	0.002	1.649 (1.100–2.471)	0.015
1985–94	75	161.3 (80.2–276.7)	–	3.607 (1.834–7.095)	0.000	1.746 (0.833–3.659)	0.140
Prior dead sibling							
No	4591	48.9 (42.8–55.5)	49.7 (42.5–57.8)				
Yes	624	106.3 (83.2–133.2)	125.8 (97.8–158)	2.374 (1.889–2.984)	0.000	2.542 (1.995–3.240)	0.0001
Milk given to last child							
Breast	4065	46.1 (39.8–53.0)	53.6 (45.8–62.3)				
Formula	576	68.3 (49.0–92.2)	78.2 (54.4–108.1)	1.402 (1.045–1.882)	0.024	1.383 (1.026–1.865)	0.033
Both	432	60.9 (40.2–87.9)	65.8 (40.6–99.8)	1.154 (0.804–1.656)	0.436	1.109 (0.766–1.603)	0.584
None given	142	318.6 (234–412)	268.3 (142–429)	6.443 (4.634–8.959)	0.000	4.459 (3.128–6.356)	0.0001

CI, confidence interval.
[a]Total number was 5215, which is the number of children born to 5169 mothers and who survived for at least 12 months before the mother was interviewed (see Fig. 1).
[b]Refers to the relative difference in mortality across the categories of the variables shown relative to the base reference category (unadjusted) and with adjustment for all the variables in the table.

high transmission rate hence reflects a series of health system failures.

The number of infants (37%) found to be exposed to HIV, and the rate amongst mothers 20–29 years of age (47%), are consistent with KwaZulu Natal Provincial HIV antenatal prevalence rates and other age-specific prevalence rates from the region [13]. That 7% of all infants at 6 weeks of age are infected is consistent with high maternal infection rates and a poorly performing PMTCT programme. Of particular concern were the women (6.9% of the DBS samples tested) who reported to be uninfected but where antibodies were present in their infants. These women perhaps chose not to declare their status (though there was little reason for them to do so), were in the window period when first tested or became infected sometime during pregnancy. Transmission rates in this group were high, 31%, which is biologically consistent with known transmission risks amongst newly infected women who have not received any intervention. If even half of these women did become infected during pregnancy then offering repeat HIV testing at 36 weeks of gestation in populations of high HIV prevalence may be cost-effective if PMTCT interventions can thereafter be made available [14].

Women who attended antenatal clinic less regularly or that delivered at home were at increased risk of transmission after adjustment for NVP. Women who lived alone were significantly less likely to have taken NVP, possibly indicating that such women would benefit from additional support. Infants of women that received nevirapine were likely to also receive nevirapine (data not shown).

We limited DBS sample collection to infants 6 weeks of age ± 2 weeks in order to avoid complicating estimates with any possible breastfeeding transmission. While it is clearly necessary to monitor the effectiveness of interventions to avert postnatal transmissions, adapting this approach for later immunization times may not be appropriate as attendance at these visits is less consistent and infected infants are likely to die even within the first 3 months of life [15]. Inconsistencies in the denominator would thus be inevitable, which would significantly undermine accurate estimates of prevalence and transmission rates.

Infant and child mortality has increased in KwaZulu Natal over the past 15 years. The populations sampled were rural or periurban communities. According to the 1998 DHS survey, the communities under surveillance were in the bottom two quintiles of socioeconomic status within South Africa. Mortality rates in these populations may, therefore, exceed national estimates. The calculated rates and trends are comparable with reported infant and child mortality rates in 2000 in KwaZulu Natal, namely 60/1000 and 86/1000 livebirths, respectively [5]. While the approach is an indirect estimate of mortality, the rates are valuable for monitoring trends and responses to interventions and will gain value in subsequent rounds of the surveillance.

Although what ultimately counts is an impact of PMTCT interventions on infant and child mortality, it is unlikely that a PMTCT programme will have any discernable impact on mortality rates within 5 years of introduction. While many social and economic factors influence infant mortality rates, these mortality data are valuable measures of comprehensive HIV care and treatment programmes that improve the well-being of HIV-infected mothers as well as reducing vertical transmission rates.

Conventional monitoring and evaluation of PMTCT programmes usually report on process indicators such as the quality of counselling or intermediate outcomes such as the number of mothers or children receiving prophylaxis. However, these are no guarantee of decreased transmissions or improved survival. The method reported provides robust data on total infection rates that can inform district managers on programme performance and be used to project the demands that should be expected of antiretroviral treatment services. The system is simple to establish and can be implemented using locally trained staff; finger/heel stab were highly acceptable to mothers. Finally, and importantly, such information could be relayed back to communities indicating the severity and impact of their 'local' epidemic.

Access to health services, which might improve the survival of HIV-infected mothers and exposed/infected children, is dependent on knowledge by individuals of their own HIV status. HIV-infected children KwaZulu Natal are rarely identified and referred to HIV care programmes when they are still asymptomatic. Linked HIV testing of all 6-week-old infants at immunization clinics could identify infected infants at an early stage and give maximum opportunity for protecting their health. It would also offer the mother another chance to learn her own status and gain access to care and treatment. The acceptability, feasibility and benefits of linked non-anonymous screening of infants at immunization clinics need to be explored. In populations with high HIV maternal seroprevalence, universal screening of infants at immunization clinics may be a justified approach to improve child survival. In the UK, routine screening for congenital hypothyroidism, using a very similar approach (i.e., heel prick onto Guthrie filter paper cards), is justified on an incidence of the condition of 1/3500 and the availability of an effective intervention. If HIV is present in up to 7% of all infants at 6 weeks and interventions are available to improve their survival chances, then would this be an acceptable and cost-effective strategy to implement at scale? The answer will be largely influenced by whether national and international agencies, clinic staff and communities can respond to the implications.

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