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\textbf{Background:} In 2000, Thailand implemented a national program to prevent mother-to-child HIV transmission (PMTCT).

\textbf{Objective:} To describe the effectiveness of the prevention of mother-to-child HIV transmission program in Thailand.

\textbf{Design and methods:} A register of HIV-exposed children at birth was created with follow-up of infection status. The register included children born to HIV-infected women between 1 January 2001 and 31 December 2003 at 84 public health hospitals in six provinces of Thailand. The main outcome measure was HIV infection in children.

\textbf{Results:} A total of 2200 children born to HIV-infected mothers were registered. Of these mother–infant pairs, 2105 (95.7\%) received some antiretroviral prophylaxis, including 1358 (61.7\%) who received the complete short-course zidovudine regimen during pregnancy and labor for the mother and after birth for the infant, with or without other antiretrovirals. HIV infection outcome was determined for 1667 (75.8\%) children, of whom 158 (9.5\%, 95\% confidence interval (CI), 8.1–11.0\%) were infected. Transmission risk was 6.8\% (95\% CI 5.2–8.9\%) among 761 mother–infant pairs that received the complete zidovudine regimen alone, and 3.9\% (95\% CI, 2.2–6.6\%) among 361 mother–infant pairs that received the complete zidovudine regimen combined with other antiretrovirals, usually nevirapine. The overall transmission risk from this cohort, including all antiretroviral prophylaxis combinations, is estimated to be 10.2\%.

\textbf{Conclusions:} The Thai national PMTCT program is effective in reducing mother-to-child transmission risk from the historical risk of 18.9–24.2\%. The addition of nevirapine to short-course zidovudine beginning in 2004 may further improve program effectiveness in Thailand.

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\textbf{Keywords:} Thailand, HIV prevention, vertical HIV transmission, antiretroviral therapy, zidovudine, nevirapine, monitoring and evaluation
Introduction

Since the epidemic of HIV infection among pregnant women began in Thailand in the early 1990s, more than 100,000 children have been born at risk for mother-to-child transmission. In 2000, following a 1995–1998 trial of short-course zidovudine (ZDV) at two Bangkok hospitals which demonstrated a reduction in mother-to-child HIV transmission from 18.9 to 9.4% [1], a 1997–1999 randomized trial of long and short-course ZDV that demonstrated transmission rates of 4.7 to 8.6% [2], and the success of regional pilot programs that demonstrated a high uptake of antenatal HIV testing and ZDV prophylaxis [3,4], the Thailand Ministry of Public Health (MOPH) began implementing a national program for prevention of mother-to-child HIV transmission (PMTCT). The program included routine HIV testing and counseling during pregnancy, and for HIV-infected women, short-course ZDV for the mother and ZDV syrup for the infant, and provision of infant formula [5,6].

Data from a national system to monitor program implementation has shown a high uptake of all program elements, including 96.7% of women receiving antenatal care (ANC), 93.3% of these with an HIV test, and 70.1% of HIV-positive women receiving antiretroviral prophylaxis prior to delivery [7]. In 2001–2002 some PMTCT sites began adding single dose nevirapine (NVP) for both mothers and infants, and in December 2003 the national regimen was modified to include single dose NVP in addition to ZDV.

To determine the effectiveness of the national PMTCT program, in 2001 the Thailand MOPH initiated population-based surveillance of the outcomes of children born to HIV-infected mothers in all public hospitals in six of Thailand’s 75 provinces. This paper, which reports on approximately 10% of all HIV-positive deliveries in Thailand, is one of the first reports of population-based mother-to-child transmission risks from a large program in a developing country.

Methods

The MOPH, with assistance from the US Centers for Disease Control and Prevention, established a hospital-based registry to collect information on children born to HIV-infected mothers who were either born in or had their HIV status determined at 84 MOPH hospitals in six provinces (Chiang Rai, Ubon Ratchathani, Petchaburi, Songkhla, Nhong Khai and Phrae), chosen to provide diversity in location and HIV prevalence among pregnant women (Fig. 1). The hospital-based registry began in January 2001 in the first four provinces, and in July 2003 in Nhong Khai and Phrae. The median HIV prevalence among pregnant women in these provinces is 1.5% and ranges from 0.7 to 2.4% (Fig. 1). The total number of deliveries at these hospitals represents 9% of deliveries nation-wide in public hospitals and 85% of all births in Thai hospitals are estimated to be in public hospitals [8].

At each hospital, the registry contains information on all children born to HIV-seropositive women at birth and when HIV status is determined, using a two-part form. The first part of the form is completed at birth and includes child’s sex; child’s date of birth; mother’s nationality; mother’s residence; name of the delivery hospital; whether or not mother received ANC; when mother learned of her HIV infection; antiretroviral prophylaxis provided during pregnancy, labor, and in the newborn period; mode of delivery; and breastfeeding during the first 1–3 days of hospitalization after birth. The second part of the form is completed when the HIV infection status of the infant is known or the infant has died or is determined to have been lost to follow-up. Information includes the dates, types and results of diagnostic testing; the child’s HIV diagnosis; and for children who died, the date of death and whether it was thought to be HIV-related. There was no attempt to link multiple births. Reports were collected at each hospital and sent to the provincial health office for data entry; final
data compilation was done at the national level. Completeness of the hospital-based registry system was determined through two surveys which compared the number of HIV-exposed infants reported to the registry with the number of infants identified in hospital logbooks.

A child was considered to be HIV-infected if he or she: (a) had two or more blood specimens that tested positive for HIV by polymerase chain reaction (PCR); (b) had one or more specimens that tested positive by two different assays (e.g., enzyme immunoassay or rapid test), drawn at age 18 months or greater; or (c) developed a documented AIDS-defining condition [9]; or (d) died and a diagnosis of HIV had not been excluded by laboratory tests. A child was considered not to be infected with HIV if he or she had two or more negative PCR results with at least one test performed on a specimen drawn at age 2 months or greater, or at least one negative HIV serologic test at any age. Antibody testing was performed on-site at participating hospitals, and PCR testing was conducted at regional laboratories.

For analysis, ZDV regimens were classified as complete, including ZDV to the mother during pregnancy and labor and to the infant after birth, or partial, which can include ZDV during pregnancy, labor, or the newborn period, but does not include all three time periods.

Data were analyzed using SAS (SAS Institute Inc., Cary, North Carolina, USA) and MS Access (Microsoft Inc., Redmond, Washington, USA) for all births between 1 January 2001 and 31 December 2003, and using follow-up data up to August 2005. Univariate analysis was performed for all variables potentially associated with HIV transmission. A multivariate model was created that included all variables found to be significant on univariate analysis. Trends in HIV transmission by birth cohort were calculated using chi-squared for trend.

The protocol for collection of routine surveillance data on children born to HIV-positive mothers follows Thai MOPHI procedures for confidentiality protection of HIV-positive persons. The surveillance report form does not collect names or personal identifiers. Patient identification numbers on the form are kept in a password-protected database and accessed only by involved government offices. This registry has been approved by the US CDC human subjects office as non-research with the primary intent being program evaluation.

## Results

Between January 2001 and December 2003, 2200 infants born to HIV-infected mothers were registered in the six provinces (median, 722 HIV-exposed births/year; range, 713–795). Of these, 2135 (97.1%) were born in these provinces, and 65 (2.9%) were born elsewhere but had their HIV status determined in these provinces. Results from the two surveys to audit the number of HIV-exposed infants reported to the registry system found that part 1 of the report was 725 of 743 (97.6%) complete in 2001 and 676 of 684 (98.8%) complete in 2003.

Characteristics of these mother–infant pairs and the program interventions they received are shown in Table 1. Further characterization of the 747 mother–infant pairs that received partial ZDV showed that 149 (19.9%) had antenatal and neonatal ZDV, 178 (23.8%) had intrapartum and neonatal ZDV, 371 (49.7%) had neonatal ZDV, and 49 (6.6%) had other or unknown parts of a ZDV regimen. Of the 483 mother–infant pairs that received other antiretrovirals, 24 (5.0%) mothers received NVP during pregnancy, 412 (85.3%) mothers received NVP during labor, and 422 (87.3%) newborns received NVP. A total of 373 of 422 (88.4%) newborns who received NVP were born in Chiang Rai or Songkhla.

As of August 2005, 1667 (75.8%) of the 2200 children had known HIV-infection outcomes. Of these, 1509 (90.5%) were uninfected, and 158 (9.5%) were infected: 84 were diagnosed on the basis of laboratory testing, 28 by clinical definition, and 46 died before infection was excluded. Among the 1593 children whose negative or positive HIV status was determined by laboratory criteria, 715 (44.9%) were diagnosed by antibody and 878 (55.1%) were diagnosed by PCR. The transmission rates by year of birth were 10.3% in 2001, 9.4% in 2002 and 8.6% in 2003 ($P = 0.32$, chi-squared for trend).

Table 2 shows the transmission rates among various subgroups. In univariate analysis, the transmission risk was significantly lower among those whose mothers had ANC (8.5 versus 22%), learned about their HIV infection during the pregnancy (7.3 versus 21.5%), or who received any antiretroviral prophylaxis (8.7 versus 37.5%). In multivariate analysis, only the use of ZDV and the addition of other antiretrovirals to ZDV were significantly associated with a lower transmission risk.

HIV-positive women who knew their HIV status before this pregnancy were less likely to get ANC (79 versus 83%; $P < 0.001$), to receive ZDV during pregnancy (55 versus 76%; $P = 0.02$) or labor (52 versus 73%; $P = 0.03$) and to be delivered by Caesarian-section (0 versus 15%; $P = 0.02$), compared with women who learned their HIV status during pregnancy. Receipt of the three-part ZDV regimen (42 versus 61%; $P = 0.07$), breastfeeding during hospitalization (3 versus 1%; $P = 0.49$), and newborn receipt of ZDV (79 versus 86%; $P = 0.36$) were not significant differently among women learning their HIV status before and during pregnancy, respectively.
Among the 533 children whose HIV status was not determined, 332 (62.3%) were lost to follow-up, 187 (35.1%) had incomplete reports, and 14 (2.6%) had discrepant laboratory results. The mothers of children who had unknown outcomes were more likely than those with known outcomes to be non-Thai (13.7 versus 7.3%), not to have had ANC (17.6 versus 6.5%), not to have taken antiretrovirals (6.8 versus 2.9%), and to have been diagnosed during labor (11.8 versus 5.0%) or after delivery (14.6 versus 6.1%) (Table 1). These associations suggest that children without known outcomes may have been at higher risk for infection than those with known outcomes.

As the multivariate analysis found only antiretroviral prophylaxis significantly associated with a lower transmission risk, we applied the transmission risks for the various strata of antiretrovirals to children without known outcomes. We estimated that there were 67 HIV infections among children without known outcomes and that the transmission risk in this group was 12.6%. Combining children with and without known outcomes, we estimate that there were a total of 225 HIV infections among the 2200 children, for an overall transmission risk of 10.2%.

Discussion

This population-based registry of infant outcomes provides one of the first reports of the success of a national PMTCT program in which routine PMTCT services are delivered as part of a national program, outside of clinical trial or study settings. Due to the difficulty of ascertaining infant infection status in resource-limited settings, it has been difficult to measure the effectiveness of routine PMTCT programs. A study by Dabis et al. in Cote d’Ivoire reported PMTCT field efficacy in a large cohort in Cote d’Ivoire. While this research study included more intensive antenatal follow-up and monitoring than is typically offered in routine PMTCT programs, 6-week transmission rates were only slightly lower than found in our registry (4.6% in Cote d’Ivoire versus 5.2% in Thailand for ZDV/NVP regimen) [10]. In addition, a WHO bulletin report by Coetze et al. reported on the field efficacy of a PMTCT program in one South African district, including 538 mother–infant pairs. Using slightly different antiretroviral regimens but predominant formula feeding, this study reported similar transmission rates to those found in Thailand (8.8% in one South African district) [11].
This registry in Thailand provides several types of useful information to improve Thailand’s PMTCT program. First, it provides additional information on the extent to which key components of the program are implemented in Thailand, including ANC, routine prenatal HIV testing, and antiretroviral prophylaxis for HIV-infected pregnant women. The finding that 61.7% of the mother–infant pairs received the complete three-part ZDV regimen was slightly less than the 68% found in a hospital-based evaluation in Bangkok [12]. The proportion of children who breastfed (2.4%) was the same as found in the Bangkok evaluation. The proportion of HIV-infected mothers that received ANC (90.0%) was lower than the average national ANC rate which is more than 95% [7]. However, the ANC rate was nearly the same as reported in a study of Bangkok women before the use of antiretroviral prophylaxis [1,16].

Second, collecting HIV infection status from infants born to HIV-infected mothers allows an estimation of transmission risk, which is a measure of the success of a PMTCT program. The efficacy of prophylactic antiretroviral interventions on reducing transmission risk has been demonstrated clearly in well-controlled study populations and pilot projects in Thailand [1,2,13,14] and elsewhere. However, determination of effectiveness of this intervention requires measuring infection outcomes when implemented in public health programs such as Thailand’s. The public health challenges in scaling up PMTCT programs are widely recognized [15]. Efforts to scale-up the PMTCT program in Thailand required strengthening the public health infrastructure; training in counseling, clinical management, and program management for staff working in over 880 public health hospitals; and mobilizing communities to support the program. Data from this surveillance system indicate that despite the challenges, the estimated population-level transmission risk is 10.2%, which is approximately 46–58% lower than the estimated 18.9–24.2% transmission risk documented in non-breastfeeding Bangkok women before the use of antiretroviral prophylaxis [1,16].

Third, we monitored the impact of a variety of antiretroviral usage patterns, including the use of NVP added to ZDV. These surveillance data suggest that the complete three-part ZDV regimen may be more effective than partial regimens and support clinical trial data indicating that the addition of NVP may further reduce the risk of transmission [13].

However, our data also show that some women who knew their HIV status prior to pregnancy still do not...

Table 2. HIV transmission risk among 1667 children born to HIV-infected mothers, by characteristic or intervention.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. HIV-infected/no. with outcome</th>
<th>Percentage infected (95% confidence interval)</th>
<th>Odds ratio</th>
<th>P-value</th>
<th>Adjusted odds ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>158/1667</td>
<td>9.5 (8.1–11.0)</td>
<td>Reference</td>
<td>0.43</td>
<td>Reference</td>
</tr>
<tr>
<td>Mother’s nationality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Thai</td>
<td>14/122</td>
<td>11.5 (6.7–18.8)</td>
<td>Reference</td>
<td>&lt;0.0001</td>
<td>Reference</td>
</tr>
<tr>
<td>Thai</td>
<td>143/1537</td>
<td>9.3 (7.9–10.9)</td>
<td>0.79 (0.43–1.48)</td>
<td>0.64 (0.35–1.18)</td>
<td></td>
</tr>
<tr>
<td>Antenatal care history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antenatal care</td>
<td>24/109</td>
<td>22.0 (14.9–31.2)</td>
<td>Reference</td>
<td>&lt;0.0001</td>
<td>Reference</td>
</tr>
<tr>
<td>Had antenatal care</td>
<td>131/1545</td>
<td>8.5 (7.2–10.0)</td>
<td>0.33 (0.20–0.53)</td>
<td>0.64 (0.35–1.18)</td>
<td></td>
</tr>
<tr>
<td>Antiretroviral intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiretroviral</td>
<td>18/48</td>
<td>37.5 (24.3–52.7)</td>
<td>Reference</td>
<td>&lt;0.0001</td>
<td>Reference</td>
</tr>
<tr>
<td>ZDV only</td>
<td>113/1189</td>
<td>9.7 (8.1–11.5)</td>
<td>0.18 (0.10–0.33)</td>
<td>0.21 (0.11–0.41)</td>
<td></td>
</tr>
<tr>
<td>Three-part ZDV*</td>
<td>52/761</td>
<td>6.8 (5.2–8.9)</td>
<td>0.12 (0.06–0.23)</td>
<td>0.14 (0.07–0.29)</td>
<td></td>
</tr>
<tr>
<td>Partial ZDVb</td>
<td>63/428</td>
<td>14.7 (11.6–18.5)</td>
<td>0.25 (0.09–0.65)</td>
<td>0.28 (0.14–0.54)</td>
<td></td>
</tr>
<tr>
<td>ZDV + other antiretroviral</td>
<td>22/422</td>
<td>5.2 (3.4–7.9)</td>
<td>0.09 (0.04–0.19)</td>
<td>0.12 (0.05–0.25)</td>
<td></td>
</tr>
<tr>
<td>Three-part ZDV + other antiretroviral</td>
<td>14/361</td>
<td>3.9 (2.2–6.6)</td>
<td>0.07 (0.03–0.15)</td>
<td>0.08 (0.04–0.18)</td>
<td></td>
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<tr>
<td>Partial ZDVc</td>
<td>8/61</td>
<td>13.1 (6.2–24.8)</td>
<td>0.25 (0.10–0.65)</td>
<td>0.22 (0.08–0.60)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>140/1415</td>
<td>9.9 (8.4–11.6)</td>
<td>Reference</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>173/245</td>
<td>6.9 (4.2–11.1)</td>
<td>0.68 (0.40–1.36)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>5/35</td>
<td>14.3 (5.4–31.0)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never received</td>
<td>147/1616</td>
<td>9.1 (7.8–10.6)</td>
<td>1.67 (0.64–4.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When mother first knew HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Before pregnancy</td>
<td>33/291</td>
<td>11.3 (8.0–15.7)</td>
<td>Reference</td>
<td>&lt;0.0001</td>
<td>Reference</td>
</tr>
<tr>
<td>During pregnancy</td>
<td>84/1154</td>
<td>7.3 (5.9–9.0)</td>
<td>0.61 (0.40–0.94)</td>
<td>0.67 (0.43–1.04)</td>
<td></td>
</tr>
<tr>
<td>During labor</td>
<td>16/83</td>
<td>19.1 (11.8–29.7)</td>
<td>1.87 (0.97–3.59)</td>
<td>1.58 (0.80–3.15)</td>
<td></td>
</tr>
<tr>
<td>After delivery</td>
<td>22/102</td>
<td>21.6 (14.3–31.0)</td>
<td>2.15 (1.19–3.90)</td>
<td>1.30 (0.66–2.55)</td>
<td></td>
</tr>
</tbody>
</table>

*Three-part zidovudine (ZDV) = ZDV used during pregnancy, labor, and newborn period.

bPartial ZDV = ZDV used during pregnancy, labor, and/or newborn period, but not all three periods.

cAll significant variables from univariate analysis were included in the multivariate analysis.
There are several limitations to our findings. First, 533 (24.2%) of the infants in our birth cohort had incomplete follow-up or inconclusive outcomes, and it appears that those without outcomes may have had a higher transmission risk due to lower uptake of antiretroviral prophylaxis. To address this data gap, we estimated the transmission risk of this population by applying the transmission risk of the antiretroviral regimens these women are known to have received. Second, the assumption that all deaths were HIV-related may have led to an overestimation of the HIV transmission risk, because some deaths may have occurred in uninfected children. Third, we did not collect data on how well the mother or infant adhered to the antiretroviral regimens or on breast-feeding practices after an infant was discharged from the hospital. Finally, our registry data were only collected from public health hospitals, and implementation in private or semi-private settings were not evaluated by this system.

This analysis has several implications for the PMTCT program in Thailand. Lack of ANC and subsequent delayed antenatal HIV testing remain a barrier to PMTCT, leading to a substantial number of mothers and babies receiving less than optimal antiretroviral interventions. The national PMTCT program is now focused on ensuring greater access to ANC and on improving the coverage of the recommended antiretroviral regimen. Second, the low transmission risk associated with complete ZDV plus NVP supports Thailand’s new PMTCT policy. Based on new research [10,13,17], the MOPH recommended that all pregnant HIV-infected women begin ZDV at 28 (rather than 34) weeks gestation, single-dose NVP be given with intrapartum ZDV, and HIV-exposed infants receive single-dose NVP at birth, along with a course of ZDV. Third, this report highlights the importance of early infant diagnosis for both medical care and program outcome evaluation. Efforts are currently underway to improve the follow-up and HIV testing of HIV-exposed children by providing free PCR testing for all HIV-exposed infants through Thailand’s universal health coverage program. Attempts to locate HIV-infected children who have been lost to follow-up are underway through community hospitals and people living with HIV/AIDS networks.

These data from the six surveillance provinces are likely to be representative of the PMTCT situation in other provinces in Thailand. The report of the Department of Health PMTCT program monitoring presents similar uptake of key PMTCT services from both the national and this six-province data (e.g., uptake of HIV testing in pregnant women = 96.1 versus 95.2% and the receipt of antiretrovirals for PMTCT = 77.0 versus 77.9% in the national and six-province data, respectively) [18]. As a result of the success of this six-province registry system, it is being expanded into other provinces that also may benefit from this type of registry.

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