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The Thailand MoPH–U.S. CDC Collaboration in Asia

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INTRODUCTION

In 1990, a joint activity between the Thailand Ministry of Public Health (MoPH) and the U.S. Centers for Disease Control and Prevention (U.S. CDC) known as the "HIV/AIDS Collaboration" was born, its primary objective was to conduct HIV prevention research to contribute to HIV/AIDS control efforts in Thailand. The Collaboration maintained an office and a laboratory on the campus of the MoPH in Nonthaburi, a Bangkok suburb. U.S. CDC scientists and public health advisors were assigned to live and work in Thailand alongside Thai MoPH colleagues. Local staff were hired and supported by the U.S. Embassy in Bangkok and the MoPH. This research initiative built on the trust established between the Thai MoPH and the U.S. CDC through the Thai Field Epidemiology Training Program (FETP), which was inaugurated in 1980, becoming the first FETP program outside North America. The Thai FETP is modeled on U.S. CDC's Epidemic Intelligence Service (EIS) program, both striving to improve public health surveillance, prevention and disease control efforts.

In 2001, Thailand became one of 25 partner countries participating in U.S. CDC's Global AIDS Program (GAP), an effort of the U.S. Department of Health and Human Services to assist countries with a high burden of HIV/AIDS by providing support for HIV prevention programs, care for persons living with HIV/AIDS, and capacity building in training, laboratory testing, surveillance, and monitoring and evaluation. Also in late 2001, the Collaboration welcomed the U.S. CDC's first International Emerging Infections Program (IEIP) to Thailand. The IEIP aims to integrate disease surveillance, applied research, training and capacity development and

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support for outbreak investigations of emerging infections. The addition of GAP and IEIP to the joint activity between the MoPH and U.S. CDC prompted a name change to the "Thailand MoPH–U.S. CDC Collaboration," which more accurately reflects the Collaboration's research and programmatic activities in HIV/AIDS, sexually transmitted infections (STIs), tuberculosis (TB), and other emerging infections.

This chapter reviews some of the Collaboration's major contributions in HIV/AIDS research over its 13-year history, and its new activities through GAP and IEIP.

HIV/AIDS RESEARCH

Descriptive Epidemiology

In 1988–1991, Thailand experienced an explosive HIV epidemic among injection drug users (IDU) and persons with sexual risk behaviors (World Bank Thailand Office, Bangkok, 2000; Weniger *et al.*, 1991; Nopkesorn *et al.*, 1993). In 1991, an analysis of HIV strains collected among high risk transmission populations across Thailand identified two distinct HIV-1 subtypes that could be segregated by transmission group (IDU, subtype B; persons with heterosexual risk behaviors including female sex workers, subtype E [later known as CRF 01_AE]), suggesting that the HIV epidemics in these two populations were largely independent (Ou *et al.*, 1993; Wasi *et al.*, 1995; Kalish *et al.*, 1995). However, this relatively clear HIV-1 subtype segregation by risk category was not sustained; by the mid 1990s, HIV-1 subtype E accounted for an increasing proportion of infections among IDU, in addition to the great majority of infections among persons with heterosexual risk behaviors (Subbarao *et al.*, 1998; Kitayaporn *et al.*, 1998; Limpakarnjanarat *et al.*, 1998). Spread of HIV from high risk groups to the general population was rapid, as evidenced by HIV prevalence among pregnant women attending antenatal clinics where HIV climbed steadily from 0.6% in 1991, peaking at 2.3% in 1995 (Kanshana and Simonds, 2002), and dropping slowly, yet steadily, to 1.4% in 2002 (Thai MoPH, 2002). Through the year 2000, nearly one million Thais became infected with HIV, with an additional 29,000 new infections estimated to have occurred in 2001; roughly 650,000 Thais are living with HIV/AIDS (CDC/Thai MoPH, 2003).

In 1988, a severe HIV epidemic was recognized among Bangkok's IDU, with prevalence rising from less than 1% to greater than 40% by years end, and later spreading to all provinces of Thailand and to other IDU populations in the Southeast Asia region (World Bank Thailand Office, Bangkok, 2000; Weniger *et al.*, 1991). Although the MoPH is rightfully touted for its success in dampening the spread of new HIV infections among female sex workers, their male clients, military conscripts, and pregnant women (Rojanapithayakom and Hanenberg, 1996; Nelson *et al.*, 1996; Kilmarx *et al.*, 2000b; Mastro and Limpakarnjanarat, 1995; Weniger and Brown, 1996; Torgusa *et al.*, 2003), the median prevalence of HIV-infection among IDU in Thailand has climbed steadily, reaching a peak of 50% in 2002 (Thai MoPH, 2002). In the absence of an effective HIV intervention targeting IDU, such as an HIV-1 vaccine, the overall proportion of new HIV infections in Thailand due to injection drug use, including women infected by needle-sharing partners, is projected to increase to 41% by 2005 (World Bank Thailand Office, Bangkok, 2000).

HIV Transmission among IDU and HIV Vaccine Evaluation

In 1991, the World Health Organization (WHO) initiated an HIV vaccine development program, including support to establish preparatory cohorts for HIV-1 vaccine trials (Esparza *et al.*, 1991; Heyward *et al.*, 1996). Simultaneously, the Royal Thai Government developed a National Plan for HIV/AIDS Vaccine Development and

Evaluation (Phoolcharoen *et al.*, 1998). With the political will of the MoPH behind it, an HIV vaccine preparatory cohort study was initiated to assess the feasibility of conducting an HIV vaccine efficacy trial among IDU at high risk for acquiring HIV infection.

In Bangkok, an extensive network of 17 outpatient narcotic clinics operated by the Bangkok Metropolitan Administration (BMA) provides free methadone treatment services annually for 6000 to 8500 IUD (Mastro *et al.*, 1994a). To assess the feasibility of conducting a large-scale HIV-1 vaccine trial in this population, the BMA, in partnership with Mahidol University, WHO, the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Collaboration conducted an HIV vaccine preparatory cohort study among IDU who were 18 to 50 years of age and attending BMA drug treatment clinics and testing negative for HIV-1 antibodies. This 1995–1998 BMA cohort study of 1209 IDU (median age, 31 years; 93% male) revealed a follow-up time contribution of 88.2% at 12 months, an annual HIV-1 incidence rate of 5.8 per 100 person-years, an HIV-1 subtype distribution of 21% B and 79% E (Vanichseni *et al.*, 2001), the clinical course of HIV infection by subtype (Hu *et al.*, 2001), the presence of intersubtype superinfections (Ramos *et al.*, 2002), and the willingness of a majority of IDU to participate in an large-scale efficacy trial (MacQueen *et al.*, 1999). The subtype distribution validated early genetic characterization work from this cohort (Subbarao *et al.*, 2000; Phan *et al.*, 2000), prompting the formulation (Berman 1998; Francis *et al.*, 1998), and safety and immunogenicity evaluation (Pitisuttithum *et al.*, 2000) of a bivalent recombinant gp120 HIV-1 vaccine (AIDSVAX®B/E; VaxGen, Inc.) made specifically for use in Thailand.

From March 1999 through June 2003, the world's first Phase III HIV vaccine efficacy trial outside the North America was conducted in Thailand by the Bangkok Vaccine Evaluation Group (BVEG), a team comprised of the BMA, Mahidol University, VaxGen, Inc., and the Collaboration. Recruitment and enrollment of 2546 HIV-negative IDU was completed in August 2000 (Vanichesni *et al.*, 2004). Volunteers received either AIDSVAX®B/E vaccine or placebo (1:1 ratio) at months 0, 1, and 6, with booster doses at months 12, 18, 24, and 30. Participants were followed for 36 months, immunization compliance exceeded 95%, and risk behavior counseling was shown to be effective throughout the conduct of the trial (van Griensven *et al.*, 2003a). Trial results were announced on November 12, 2003 (VaxGen, 2003); the vaccine failed to demonstrate efficacy for the prevention of HIV infection, and failed to demonstrate mitigation of clinical HIV disease progression prior to the initiation of highly active antiretroviral drug therapy (HAART), which was universally provided according to BMA treatment guidelines (Martin *et al.*, 2003). Although trial results were disappointing, the vaccine preparatory cohort and vaccine trial were successful in increasing Thailand's capacity to conduct future HIV vaccine trials, and proved that high-risk populations, such as IDU, can ethically participate in the evaluation of promising HIV vaccine candidates in large-scale trials.

Prevention of Mother-to-Child Transmission of HIV

Since 1992, the Collaboration has worked with the MoPH, Mahidol University, and other partners to conduct research directed at understanding and preventing mother-to-child HIV transmission (PMTCT). Early retrospective, descriptive work identified HIV infection to be an important factor for low birth weight deliveries (Srismith *et al.*, 1998), and that HIV prevalence at delivery increased rapidly from 1.3% in 1990 to 6.4% in 1994 (Bunnell *et al.*, 1999) in Chiang Rai province. Having more than one lifetime sex partner was found to be an important risk factor for HIV infection among pregnant women delivering at two large hospitals in Bangkok, and surprisingly, a quarter

of all delivering women had current partners who were not HIV-infected (Siriwasin *et al.*, 1998). A prospective study of mother-to-child HIV transmission in these two hospitals during 1992–1994 found the risk of transmission to be 24.2% (Shaffer *et al.*, 1999b), with 75% of these infections arising intrapartum (Mock *et al.*, 1999), and with maternal viral load being the strongest predictor for transmission for both in utero and intrapartum transmission.

In 1994, the results of AIDS Clinical Trials Group (ACTG) protocol 076 were announced (Conner *et al.*, 1994). The study found that a complex regimen of zidovudine (076 regimen), given to HIV-infected women during pregnancy, labor and to the neonate for 6 weeks reduced mother-to child transmission by two-thirds in the absence of breastfeeding. However, most HIV-infected women live in Africa and Asia in settings where governments (including Thailand) could not afford the 076 regimen implementation costs (Stringer *et al.*, 1999). In order to find a safe, simple, and inexpensive regimen, the Collaboration, building on the infrastructure established during the 1992–1994 study, conducted a Phase III, randomized, placebo-controlled clinical trial of short-course zidovudine for PMTCT in Bangkok in 1996–1998 (CDC, 1998; Shaffer *et al.*, 1999a). HIV transmission was significantly lower (9%) among the 198 women who received zidovudine from 36 weeks' gestation until labor onset, then every 3 hours until delivery, than among the 199 women who did not (19%); adverse events were similar in the 2 groups (mild anemia at birth only), as was survival among HIV-infected children at 18 months follow-up (Chotpitayasunondh *et al.*, 2001). The trial results had a profound and immediate impact on Thailand and the world (Kanshana and Simonds, 2002). Several weeks after the results were announced, UNAIDS met and issued a recommendation to use the short course zidovudine regimen in countries that could not implement the 076 regimen. Additional findings from this trial included the detection of HIV in cervicovaginal lavage (CVL) specimens as an independent risk factor for mother–child transmission (Chuachoowong *et al.*, 2000), and the evaluation of the sensitivity and specificity of the Roche Amplicor RNA and DNA PCR tests for early diagnosis of HIV-1 infection (Young *et al.*; 2000); RNA PCR was more sensitive (47%) at birth than DNA PCR (38%), and both assays were 100% sensitive and specific by two months of age.

Since the late 1990s, nevirapine has received increasing attention in Thailand for PMTCT (either in combination with short-course zidovudine, or as an alternative to the 1- or 6-week infant component of modified national zidovudine regimen (Amornwichet *et al.*, 2002) due to its low cost, favorable pharmacokinetics, and simplicity and efficacy as monotherapy. Because there is limited data on the safety or efficacy of nevirapine in Thai women and children, the Collaboration conducted a Phase II, single-arm, open label clinical trial of providing nevirapine to 220 mothers and their children already receiving the short-course zidovudine regimen. Mothers received one 200 mg dose of nevirapine after presenting to the hospital in labor, and their infants received one 6mg (approximately 2 mg/kg) dose in the first three days of life. The perinatal transmission rate was 4.6%, and 93% of women had blood specimens that tested successfully for drug resistance; of these, 17% and 2% had nevirapine and zidovudine resistance mutations, respectively (Chaowanachan *et al.*, 2003). Data from this trial and others in Thailand prompted the MoPH to add nevirapine to the national short-course zidovudine regimen in late 2003.

Sexual Transmission of STIs, HIV, and the Study of Vaginal Microbicides

In 1991, the Collaboration established a field research station in Chiang Rai, Thailand's northernmost province where HIV infection rates have been among the highest in Asia (Kilmarx *et al.*, 2000b). Surveillance data from the first half of the decade found increasing prevalence of HIV infection

among all risk groups, and in particular, female sex workers (Limpakarnjanarat *et al.*, 1991). STIs were common among female sex workers from Chiang Rai who were followed in a prospective cohort study. (Kilmarx *et al.*, 1998b; Limpakarnjanarat *et al.*, 1999), More than half were using medications they obtained from a source other than a STI clinic, such as a pharmacy, to treat symptomatic disease (Kilmarx *et al.*, 1997). From 1991–1994, HIV incidence among 285 female sex workers in this Chiang Rai cohort was 20.3 per 100 person-years among 126 brothel-based sex workers and 0.7 per 100 person-years among 159 sex workers who worked in other venues; risk factors for acquiring HIV infection were working in a brothel and having chlamydia cervicitis (Kilmarx *et al.*, 1998b). In addition, some female sex workers were using vaginal products with the perception that they might help to prevent STIs, rather than potentially facilitating acquisition of HIV/STI through damage to the vaginal and cervical mucosa (Kilmarx *et al.*, 1998a). Sex work was also found to be inconsistent, with a majority of sex workers having one or more quit-re-entry-quit cycles. These inconsistencies were determined by economic factors, relationship with a steady partner, attitudes towards sex work, and HIV/AIDS experience (Manopaiboon *et al.*, 2003). Disease progression and survival rates among 194 female sex workers in this cohort with HIV infection (96% subtype E) were shown to be similar to that found among populations elsewhere with HIV subtype B infection (Kilmarx *et al.*, 2000a), and the mortality risk among HIV-infected sex workers was more than 50-fold higher when compared to sex workers without HIV infection (Kilmarx *et al.*, 2000c). This cohort also provided the opportunity to identify genetic polymorphisms, such as HLA-A11, CCR5 59402GG promoter, and SDF-1 3′ UTR 801 A (Sriwanthana *et al.*, 2001), homozygosity of HHF*2 (the CCR2b-641 bearing haplogroup [Yang *et al.*, 2003]), and viral suppressive activity (Butera *et al.*, 2001) that might explain resistance to HIV infection among highly HIV-exposed, persistently seronegative female sex workers.

A 1991–1993 prospective cohort study of more than 1100 young, male military conscripts from northern Thailand identified sex with female sex workers as the dominant risk factor for HIV infection and identified other STIs as a major co-factor for transmission (Nopkesorn *et al.*, 1993; Nopkesorn *et al.*, 1998). A subsequent study also identified a relatively high per-sex-act HIV-1 transmission probability from female sex workers to young men, perhaps explaining in-part the rapid expansion of the HIV-1 epidemic in northern Thailand (Mastro *et al.*, 1994b) Although the "100% condom" campaign was effective in rapidly decreasing HIV prevalence among young male military conscripts (Rojanapithayakom and Hanenberg, 1996; Nelson *et al.*, 1996; Kilmarx *et al.*, 2000a; Mastro and Limpakarnjanarat, 1995; Weniger and Brown, 1996; Torgusa *et al.*, 2003), HIV prevalence remained high among our cohort of 508 women who entered sex work at different time intervals throughout the 1990s, suggesting ongoing infection risk in this population (Kilmarx *et al.*, 1999).

Vaginal microbicides are a promising new technology that if effective, could be used by women to protect themselves from infection with HIV and other STIs. Carraguard® (with 3% carrageenan), is the Population Council's lead candidate microbicide. Carrageenans are sulfated polymers with a large molecular weight derived from seaweed, and have been used extensively in the food, pharmaceutical, and cosmetics industries. Carraguard® has been shown to block infection from HIV and other STIs, and is thought to be noncontraceptive. A randomized, placebo-controlled, Phase II study of Carraguard® among 165 HIV-seronegative women was completed in Chiang Rai in December 2001, and a second Phase II clinical trial of this product among 55 HIV-seronegative couples was completed in Chiang Rai in June, 2002. Preliminary, blinded results from both studies revealed

strong safety profiles and high rates of acceptability with product use (Manopaiboon *et al.*, 2002; Limpakarnjanarat *et al.*, 2002; Kilmarx *et al.*, 2002; Blanchard *et al.*, 2004; Kilmarx *et al.*, 2004). Some women who choose to use a microbicide may be HIV-infected, but may not be aware of their infection. Therefore, data from microbicide studies of HIV-infected women are important. Enrollment into a third Phase II trial of Carraguard® among 54 HIV-infected women in Chiang Rai was completed in March 2004 (McLean *et al.*, 2004b; McLean *et al.*, 2004a; Chaikummao *et al.*, 2004). Final, unblinded analyses for these three studies will be conducted following completion of companion studies in South Africa; results will be critical for moving forward the Population Council's planned Phase III efficacy trial of Carraguard® in South Africa. Heterosexual women attending postpartum and family planning clinics in Chiang Rai have low (3.1%) HIV prevalence (Xu *et al.*, 2002), and although they have expressed a willingness to participate in large-scale vaginal microbicide trials (Tharawan *et al.*, 2001), their annual incidence of HIV infection in not sufficient to conduct a Phase III trial (Xu *et al.*, 2000; Tharawan *et al.*, 2001; Xu *et al.*, 2002). The Phase II evaluation of promising new vaginal microbicide candidates, as well as other studies will continue in Chiang Rai with the strong support of the Provincial Public Health Office and Chiang Rai Regional Hospital.

Behavioral Science

In 1998, a behavioral science section was added to the Collaboration to increase behavioral research capacity, provide support for the development of procedures for protection of human subjects in research and to monitor risk behaviors in HIV clinical trials. In 1999, a rapid assessment of the "Prevalence of HIV, STD and sexual and drug use Risk behaviors among Adolescents and Young Adults" or PHRAYA Study was conducted in Chiang Rai (van Griensven *et al.*, 2001). In this study, an innovative audio-computer-assisted self-interviewing (ACASI) technique was used in conjunction with non-invasive HIV, STI and drug use testing methods (oral fluid and urine). The study enrolled 1725 students, and showed that northern Thai youth are at high risk for unsafe sex, early sexual initiation, unwanted pregnancy, STIs, sexual coercion, methamphetamine drug use and absence of motor cycle helmet use (Jenkins *et al.*, 2002; Allen *et al.*, 2003; Manopaiboon *et al.*, 2004b; Manopaiboon *et al.*, 2004a; Paz-Bailey *et al.*, 2003; van Greinsven *et al.*, 2003b; Sattah *et al.*, 2002; Pitaktong *et al.*, 2004). Although the study showed that ACASI provided high quality behavioral data, ACASI systems are relatively expensive and not easily transported.

In 2002, the Collaboration evaluated the reliability of use of hand-held mini-computers for behavioral risk surveillance among Chiang Rai adolescents (PalmPHRAYA study). In a randomized design, 1300 students were assigned to one of four data collection arms: face-to-face interview (FFI), self-administered questionnaire (SAQ), ACASI, and Palm-assisted self-interview (PASI). The study included drug-use urine testing to evaluate completeness of self-reports and reliability across arms. The PASI was found to be equivalent to ACASI, and both were superior FFI and SAQ in providing accurate and complete data to sensitive behavioral questions, and with fewer errors. Ongoing adolescent behavioral risk surveillance using PASI data collection methods is now under development with the MoPH. The low prevalence of methamphetamine use reactive urines in the PalmPHRAYA study, compared to the PHRAYA study (10.3% vs. 2.4%), prompted a qualitative assessment into trends in adolescent drug use, the results of which are currently being analyzed.

In April and May 2003, the behavioral section led the first cross-sectional assessment in men who have sex with men (MSM) in Thailand. In this venue-based assessment, 1121 MSM completed an

interviewer-administered Palm based questionnaire and oral fluid specimens were collected for HIV testing. In this young (median age 26 years) and sexually active population (22% had recent sexual intercourse with a women), an HIV prevalence of 17.3% was found, which was associated with indicators of sexual activity and lower education. This data is essential to inform and develop preventive interventions and services for this group. In addition to research among adolescents and MSM, the behavioral science section was included in several studies in groups at elevated risk for HIV infection such as Myanmese migrants (Srithanaviboonchai *et al.*, 2002), fishermen (Entz *et al.*, 2001) and drug users with a history of incarceration (Buavirat *et al.*, 2003).

GLOBAL AIDS PROGRAM (GAP)

In 2001, GAP became a component of the Collaboration, with a mission of technical cooperation with the MoPH and BMA to strengthen programs for HIV/AIDS, TB, and STI prevention and care. Thailand is one of the 25 countries supported by CDC through this program. To develop GAP activities in Thailand, the Collaboration built on its existing strengths in epidemiology, laboratory science, and informatics; on existing relationships with the MoPH and BMA that were developed through many years of collaborative research; and on findings that emerged from research performed by the Collaboration and elsewhere that were important to introduce into programs.

Although Thailand already had great success in the 1990s with HIV prevention through the program for 100% condom use (Mastro and Limpakarnjanarat, 1995; Hanenberg *et al.*, 1994) and a model program for prevention of mother to child transmission, major challenges in prevention and care for HIV/AIDS, TB, and STIs were apparent in 2001 when GAP became part of the Collaboration. The new systems for monitoring coverage and impact of activities for PMTCT needed to be strengthened and institutionalized. HIV seroprevalence among IDU remained 40–50% in Bangkok (BMA) and elsewhere around the country (MoPH), and no program of community-based outreach for IDU was in place. In early 2000, data from behavioral surveillance performed by the MoPH indicated that rates of condom use, particularly among indirect sex workers (e.g., sex work occurring in relation to bars and massage parlors), were declining, coinciding with decreased support for prevention programs at the provincial level in some areas. Concerns regarding risk behavior in adolescents were growing based on behavioral surveillance data and studies such as the PHRAYA study that demonstrated high rates of unprotected sex, unwanted pregnancy, drug use and STIs in school-age adolescents (van Griensven *et al.*, 2001). Single and dual antiretroviral therapy regimens for treatment of HIV infection had become available in some provinces in the 1990s through programs of the MoPH, and a major program was undertaken to develop comprehensive HIV/AIDS care services. However, coverage and quality of these care and treatment services was limited, even as the government was developing plans to scale-up the availability of HAART through a combination drug produced by the Thai Government Pharmaceutical Organization (GPOvir), consisting of D4T, 3TC, and nevirapine. Thailand ranked 16th among the 22 TB high-burden countries identified by WHO, and coverage of programs for directly observed therapy, short-course (DOTS), and isoniazid prophylaxis for persons with HIV infection were low (World Health Organization , 2003). Although STIs had reportedly declined dramatically over the last decade, and rates of serologic syphilis were low, utilization of sensitive diagnostic testing for chlamydia infection, which is probably the most common bacterial STI in Thailand, were not generally available.

The GAP/Thailand 5-Year Country Plan, developed in collaboration with, and approved by the MoPH in 2002 calls for 1) supporting

the work of the Departments of the MoPH centrally and 2) providing support for the development of province-level networks for support of activities in HIV/AIDS prevention, care, training and surveillance. The decision to develop mechanisms at the provincial level to strengthen technical work of HIV/AIDS, TB, and STI prevention and care by focusing initially on the development of activities in four to five provinces was based on the need to develop local models for addressing multiple complex issues in prevention and care. A major focus of the plan is on piloting new models, scaling up successful pilot projects nationally, and in some cases, filling gaps in existing programs. The major offices of the MoPH supported through GAP/Thailand are the Department of Disease Control (Bureau of AIDS, TB, and STI, and the Bureau of Epidemiology, which conducts national HIV/AIDS surveillance), and the Department of Health, (which is responsible for maternal and child health).

The first provinces selected for GAP/Thailand support in 2002 and 2003 were Bangkok, Chiang Rai, Ubon Ratchathani, and Phuket. The Collaboration's existing relationships with the BMA through the work on the BVEG AIDSVAX®B/E trial (Vanichesni *et al.*, 2004) led to the development of a new set of GAP-supported projects for strengthening HIV/AIDS programs in Thailand's largest city, with a major focus on interventions for IDU. Chiang Rai, one of the provinces most severely affected by HIV/AIDS in the 1990s, served as a key field site for collaborative research; longstanding relationships with the provincial health office and local hospitals made this a logical choice. Ubon Ratchathani was the first province to pilot the short course zidovudine intervention for PMTCT, with the support of the Collaboration for implementation and monitoring. Phuket was selected for support because of its increasing antenatal prevalence of HIV, high rates of TB, burgeoning populations of male and female sex workers, indigenous IDU and a large and transient Myanmese population with high rates of disease.

To support these activities, GAP/Thailand efforts are organized through seven technical areas: 1) training, communications and partnerships, 2) care and counseling, 3) prevention and care for families, 4) prevention and care for special populations, 5) surveillance, monitoring and evaluation, 6) laboratory services, and 7) informatics. These areas provide the structure for supporting a focused set of projects to strengthen MoPH activities, and are administered through GAP Coordinating Units established within the MoPH and BMA to administer cooperative agreement projects that address the following issues:

Preventing Mother-to-Child HIV Transmission

Activities to strengthen the national PMTCT program include support for the perinatal HIV implementation monitoring system, evaluation of a system for analyzing outcomes in infants, and two training programs to support the PMTCT program, in the context of evolving guidelines and the needs of health care workers and program managers.

Following the success of the short-course zidovudine study in 1998, the MoPH developed a plan to pilot the implementation of the short course regimen and provision of infant formula in a region covering seven northeastern provinces, where antenatal prevalence was about 1% (Kanshana *et al.*, 2000). The Collaboration was asked to work with the MoPH to evaluate this initial implementation, with the purpose of assessing the feasibility, effectiveness, and acceptability of a program consisting of routine antenatal counseling and voluntary HIV testing, zidovudine provided from 36 weeks' gestation and during labor, and free powder for preparation of infant formula for 12 months. This evaluation demonstrated that from July, 1998–June, 2000, 104,393 (86%) of 122,094 antenatal clinic clients had received HIV testing, 640 (69%) of HIV-infected pregnant women received antenatal zidovudine prophylaxis (CDC, 2001).

Analysis of HIV PCR testing performed on exposed infants after one month of age demonstrated that about 8% of infants whose mothers had received zidovudine were HIV infected, compared with 14% of infants whose mothers had not received zidovudine (CDC, 2001).

By 1999, HIV counseling and testing, zidovudine, and use of infant formula were used in many hospitals throughout Thailand for PMTCT, and in October 2000, a national system was established to monitor key PMTCT program indicators, with financial and technical support from the Collaboration. The system included logbooks maintained at the hospitals, monthly reports sent to provincial health offices where the data was computerized, regional aggregation of this data by 12 Health Promotion Centers, and final analysis and reporting by the MoPH in Nonthaburi. Standardized reports at each level were used to monitor coverage of each of the key components of the intervention. Data reported from October, 2000 through September 2001 demonstrated that of 93% of women receiving antenatal care were screened for HIV, 70% of HIV-positive women identified during screening received zidovudine before delivery, and 89% of HIV-exposed infants received prophylactic zidovudine and 83% were placed on infant formula (Amornwiclet *et al.*, 2002).

HIV/AIDS Care and Treatment

Support for the national program for improving access to care includes 1) development of systems for performance measurement of HIV care and treatment services, complemented by activities to improve the quality and coverage of these services, 2) expansion of CD4 testing, including provision of reagents and strengthening of laboratory quality assurance mechanisms, and 3) development of a model for ensuring referral of HIV-positive women identified during pregnancy, their infants, and partners into HIV care services. An initial GAP-supported assessment of HIV care and treatment services provided through public hospitals and community health centers in three northern provinces identified specific benchmarks for monitoring opportunistic infection prophylaxis, coverage, and antiretroviral therapy access (Lertpiriyasuwat *et al.*, submitted).

TB Surveillance and Strengthening of DOTS

Support is provided for strengthening TB surveillance and control activities and laboratory activities in Network provinces, and strengthening of systems for diagnostic testing, laboratory quality, and information systems at the National TB Reference Laboratory. Laboratory development includes an emphasis on increasing the availability of rapid TB culture and identification methods to facilitate surveillance and control activities. Increasing HIV testing of persons with TB is an important GAP/Thailand and MoPH objective.

STI Care

Support is provided for strengthening systems for STI care in Network provinces, and for increasing diagnostic and informatics capacity of the Division of STI. These activities include increasing the availability of diagnostic testing for *Chlamydia trachomatis* infection, which has been found in several studies to be the most common bacterial STI in Thailand, and increasing STI and cervical cytologic screening among HIV-positive women.

Interventions for IDU

A comprehensive set of assessments and interventions will be supported in Bangkok, including 1) estimation of the size of the IDU population, 2) a qualitative study of midazolam injection, 3) development of a program of community-level outreach for IDU, 4) an adult immunization program for prevention of hepatitis B and tetanus, and 5) strengthening

of the system of HIV/AIDS care for Bangkok IDU, including support for a program to provided directly observed HAART to IDU with advanced HIV disease.

Interventions for Adolescents

Support is provided to strengthen interventions for adolescents, which have become a high priority for the MoPH, due in part to the findings of the Collaboration regarding increasing rates of unprotected sexual intercourse and high rates of STIs in adolescents (van Greinsven *et al.*, 2001). GAP/Thailand is providing support to the MoPH in designing and implementing a comprehensive clinical services model for youth in four provinces.

Surveillance, Monitoring, and Evaluation

Support is provided for reviewing existing AIDS surveillance activities, and developing new models for surveillance. This will include piloting implementing the use of the personal digital assistant or hand-held minicomputer for behavioral surveillance, evaluating the role of the IgG-capture, HIV-1 subtype B, E, and D enzyme immunoassay (or BED assay) (Parekh *et al.*, 2002) for incidence estimation as a component of national HIV serosurveillance, and development of population-based surveillance for TB. GAP/Thailand is also working with the MoPH to develop systems to monitor and evaluate GAP activities, and provide support to strengthen monitoring and evaluation capacity of the MoPH and National AIDS Committee.

Through a cooperative agreement between CDC and the American Red Cross, support was also provided to the Thai Red Cross AIDS Research Centre to expand their highly successful model for anonymous voluntary counseling and testing for HIV in Bangkok to three other provinces, and to include provision of CD4 testing to facilitate entry into the growing national systems for provision of opportunistic infection prophylaxis and antiretroviral therapy. Additionally, agreements were developed with the UNAIDS Regional Office in Bangkok to use GAP funds available through UNAIDS in Geneva to strengthen activities for public-private partnerships in the fight against AIDS in the Asia region, and to advocate for interventions for prevention and care of men who have sex with men in Cambodia, Thailand, and Vietnam.

CDC GAP ASIA REGIONAL ACTIVITIES

In 2002, the Collaboration received support from U.S. CDC to establish an organized program of regional activities. The first major event was a meeting held in Chiang Rai in December, 2002, attended by representatives from GAP country offices, senior ministry of health counterparts from China, Cambodia, India, Thailand and Vietnam, and representatives of UNAIDS, USAID, and Department for International Development (DFID) of the UK. At this meeting each country provided information on potential areas for regional collaboration, focusing on key topics in surveillance, monitoring and evaluation, laboratory services, informatics, prevention (including prevention of mother-to-child transmission) and care and treatment (CDC, 2003). The U.S. CDC designated GAP/Thailand as the GAP Asia Regional Office to continue to work with other countries of the region in developing this program, which will have an important role in facilitating country-to-country collaboration, and multi-country trainings, workshops, and projects (CDC, 2003).

Vietnam

CDC activities in Vietnam in support of HIV/AIDS prevention and care were initiated in 1999, two years prior to establishment of a GAP office in that country. Initial activities included a variety of multi-disciplinary HIV training courses and technical assistance to strengthen HIV surveillance and to conduct innovative assessments to better characterize the epidemic, especially among high-risk groups such as IDU and female

sex workers. CDC supported Harvard Medical School to assist with training on HIV care and treatment and to establish VCHAP, the Vietnam-CDC-Harvard Medical School AIDS Partnership. The CDC/GAP office in Hanoi provides, through a cooperative agreement with the Ministry of Health, support to ten institutes of the Ministry and 40 provinces. The collaboration covers several areas in HIV prevention and care, with particular emphasis on voluntary counseling and testing; community outreach to high risk individuals through peer education programs; HIV treatment infrastructure including diagnosis, prophylaxis, and treatment of opportunistic infections; and support for HIV sentinel surveillance and STI surveillance.

Cambodia

A CDC/GAP assessment in Cambodia performed in 2001 recommended strengthening laboratory capacity for HIV and STI at the National Institute of Public Health and the National Center for HIV/AIDS, Dermatology, and STIs (NCHADS); supporting blood safety policy and program development, national capacity for monitoring and evaluation, a province-wide demonstration project that integrates prevention and care strategies, and training for capacity development (e.g., field epidemiology, laboratory, and program management). The CDC GAP office, established in 2002, worked directly with NCHADS to strengthen activities at the National Institute of Public Health, strengthen national STD clinical services, and develop an integrated model for interventions in Bantey Meanchay province, a province on the Thai border with high rates of HIV, TB, and STIs.

India

The GAP office in India was established in October 2001, with the primary goal of promoting integration and access to quality HIV/AIDS care and prevention in Tamil Nadu and elsewhere in India. Major activities have focused on building capacity and infrastructure for information systems and clinical and laboratory diagnosis, developing models for home-based community care, strengthening voluntary counseling and testing services, promoting a safe blood supply, and supporting training for HIV/AIDS care and prevention.

China

GAP activities in China were initiated in 2003, with establishment of a country office and a cooperative agreement with the Ministry of Health, focusing on strengthening interventions for injection drug users in heavily affected counties, with a primary emphasis on strengthening HIV serosurveillance, services for voluntary counseling and testing, and aspects of care and support. Strengthening of linkages between the China CDC and provincial and local systems for addressing the HIV/AIDS epidemic is an important focus of this effort.

INTERNATIONAL EMERGING INFECTIONS PROGRAM

CDC's first IEIP was launched in Thailand in October 2001. IEIPs were envisioned to be a center of excellence that would integrate disease surveillance, applied research, prevention and control activities (Dowell and Levitt, 2002). IEIP/Thailand maintains its relations with medical research institutes, local universities, the Thai FETP, U.S. military laboratories and WHO country and regional offices. IEIP/Thailand will strengthen national public health capacity and provide hands-on training in laboratory science, epidemiological science, and public health administration (Dowell *et al.*, 2004).

The long-term goal of the IEIP is to develop sustainable, in-country capacity for disease surveillance, outbreak investigation, and research on diseases of national, regional, or global importance by fostering the next generation of international public health leaders. In its initial years of operation, IEIP/Thailand initiated activities in each of the four priority

areas described by CDC's global strategy: surveillance, research, training and capacity development, and outbreak support.

Surveillance

IEIP/Thailand initially focused its effort on establishing population-based surveillance as one of its core objectives. With additional support by CDC, the MoPH conducts high-quality surveillance and produces data to guide national and global infectious disease control priorities (Kanlayanaphotporn *et al.*, 2004, Olsen *et al.*, 2003a). The surveillance system also provides a broad platform to launch research projects and possibly evaluate new vaccines or other interventions in the future. Provinces are selected as sites for surveillance on the basis of several criteria, including representativeness of the Thai population, accessibility from Bangkok, feasibility of capturing the majority of hospitalizations through public health systems, availability of basic laboratory facilities, existence of epidemiologic capability, and interest and commitment from local public health authorities. Sakaeo province, with a population of 613,585, located 300 kilometers east of Bangkok on the Cambodian border was chosen by a MoPH and IEIP team in March 2002 as the first site. The province established a working group to conduct a review of existing systems and proposed data collection in consultation with a CDC expert, and developed a written action plan. Case reporting began in August 2002. Pneumonia was used as the first syndrome for this phase of surveillance since it is a leading cause of mortality worldwide and hospitalized patients may be infected with any of several pathogens. Some of these organisms are also leading opportunistic pathogens among HIV infected patients in Thailand. In July 2003, Nakorn Phanom province, with a polulation of 626,221, in the northeastern region, bordering Laos was selected to be the second surveillance site. In 2003, IEIP and collaborating MoPH and provincial health offices agreed to add jaundice as a second syndrome for surveillance. Over the next few years, Thailand may be able to share expertise in emerging infections with neighboring countries.

Research

IEIP sites are intended to provide platforms for conducting a broad range of research on infectious diseases of global importance. Priority for research in IEIP sites is placed on diseases that are identified by MoPH as important public health problems in the region. In 2001, the first research project was developed in response to a request from the Thai government to assist with an ongoing epidemic of leptospirosis (Tappero, 2002; Sejvar *et al.*, submitted). A subsequent project is evaluating field diagnostic tools for use at the hospital or national level and attempting to identify new pathogens that contribute to fever. During the first year, 749 febrile patients were enrolled at the four study hospitals and 98% returned after 4 to 6 weeks to provide a convalescent serum sample and complete the final questionnaire (Fisk *et al.*, 2003). Research plans for 2002–2003 included studies of encephalitis, respiratory pathogens, and hepatitis. Collaborative research projects ultimately improve surveillance, outbreak response, and control of priority communicable diseases. At the same time, they provide training in research strategies and principles that can later be applied to future emerging diseases and be transferred to other regions of the world.

Training and Capacity Development

Capacity development through training is a priority goal of IEIP. Training through IEIP includes opportunities for scientists from Thailand to obtain advanced training in CDC laboratories and for CDC scientists to obtain training and experience in an international setting. In its first year of operation, IEIP/Thailand developed capacity through training in laboratory science, epidemiology,

case management and project management. In addition, in response to letter hoaxes with white powders purported to contain anthrax spores in late 2001, IEIP/Thailand conducted an anthrax training course with WHO's Southeast Asia Regional Office and the Thai National Institute of Health for 64 participants from 16 countries (Simmerman *et al.*, 2002).

Outbreak Support

Bringing advanced laboratory diagnostic capability to a sophisticated field investigation is one way in which IEIP can further strengthen the already existing Thai capacity for outbreak investigation, especially of unknown etiology. In 2002, IEIP assisted MoPH in investigating outbreaks of gastroenteritis among foreign tourists at a resort hotel in southern Thailand and hand, foot, and mouth syndrome in Bangkok and six other provinces. The potential for IEIP to strengthen the outbreak response to emerging infections was realized during the recent outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003. Epidemiologists from the Collaboration and the Thai MoPH worked together to set up mobile evaluation and training teams with checklists and information packets on infection control practices (Lee *et al.*, submitted). The first SARS patient in Thailand was confined to a negative pressure room with full personal protective equipment for all health care workers (Wongsawat *et al.*, 2004). Some 70 persons had contact with the patient but there were no secondary infections. Specimens from this patient were shipped to CDC and were the source for the first identification of a novel coronavirus as the cause for the worldwide outbreak (Ksiazek *et al.*, 2003). In part because of those efforts, Thailand was better able to control the spread of disease. IEIP/Thailand also served in a variety of roles for a regional SARS outbreak response, sending teams immediately in response to urgent requests from Taiwan, Laos, Hong Kong, Beijing and Singapore (Lee *et al.*, submitted; Twu *et al.*, 2003; Lim *et al.*, 2004). This regional perspective on the SARS outbreak response made possible the assembly of data from four countries on the transmission of SARS aboard aircraft (Olsen *et al.*, 2003b), and a report on differences in infection control practices in several countries (Lee, *et al.*, submitted).

CONCLUSION

For more than two decades, the Thai MoPH and U.S. CDC have worked closely together on public health and epidemiology training, capacity building, surveillance, prevention and clinical research, and public health program development. What started as general epidemiologic training in the 1980s, became focused on the exploding Thai HIV/AIDS epidemic in the 1990s, and has now broadened in the current decade to include diverse emerging infection threats in Thailand and Asia regional activities. The Thai MoPH–U.S. CDC Collaboration can serve as a model of international cooperation and capacity building with manifold benefits to public health in Thailand, Asia, and the world.

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