Life by Luck of the Draw

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LAMPANG, Thailand -- In this small city in northern Thailand, a group of pregnant women signed up for an experiment overseen by a U.S. Army doctor who sought to monitor the transfer of HIV infection to newborns.

His passive, observational study offered the women no medicine to prevent HIV transmission in order to give researchers "a more efficient and effective means" of studying them, he wrote in a memorandum. Twenty-two infants were born HIV positive to the unprotected mothers.

At a spartan drug clinic in the heart of Bangkok, heroin addicts lined up on a recent morning to receive an experimental HIV vaccine produced by an American company. Drawn by small payments and offers of free rice, they signed on for a test in which they had a greater chance of receiving a placebo -- or dummy shot -- than would Americans taking part in the same research in the United States.

In Bangkok's two largest maternity wards, pregnant women infected with HIV, the virus that causes AIDS, enrolled in an American test aimed at reducing AIDS transmission from mothers to children. But half the Thai women were given placebos instead of a proven drug, and 37 babies who might have been spared were born HIV-positive.

Set against a staggering AIDS epidemic, the Thai cases highlight the unequal bargains underlying the recent boom in overseas drug testing by both private and public medical researchers: rich countries have the drugs and hypotheses, while poor countries have vast numbers of patients. Yet the trade-offs made in experiments do not always distribute burdens and benefits evenly.

Medical progress has always depended on some individuals bearing personal risk for society's benefit. Placebos give researchers a clearer view of which experimental therapies work and which do not, many scientists contend. Passive studies that track how a disease moves unimpeded through a population can provide insights into treatment and prevention.

But those long-standing research methods have become more complicated and controversial as scientists from wealthy nations increasingly work amid poverty in developing countries. Such tests have spurred angry debate on review boards of American universities, in the halls of African and Asian health ministries and in chambers of the World Health Organization.

Among the questions: When Western researchers travel to impoverished countries to set up drug experiments, which country's ethical guidelines should apply? While working with poor test subjects, must researchers provide the best treatment available in wealthy countries? Or are they free merely to provide the best local care available -- which in some medically deprived settings may mean some test subjects get no treatment at all?

With 800,000 adults of its 61 million residents carrying the virus, Thailand's vast HIV-infected population has spent the last five years on these ethical and scientific frontiers. Open, increasingly democratic and cooperative

with the West, Thailand discovered a scourge of AIDS in its midst a decade ago and turned emphatically to its wealthy allies for help.

In 1991, the WHO designated Thailand as a country ripe to test AIDS vaccines, sowing the seeds of research still underway. In 1994, WHO issued a second challenge, encouraging researchers to help developing countries find an affordable, practical alternative to the costly Western method of reducing the transmission of HIV from pregnant women to their infants.

After each appeal, researchers armed with new drugs and theories fanned out through the country. Testing new treatments against placebos, as many did, generated fast answers. But for the men, women and children recruited into such tests, the approach meant the luck of the draw determined who received care and who wound up with nothing.

Many in Thailand tried to "look at the bright side and accept that when you are a poor people you may have the choice between getting some treatment and care in a study or having none," said Vichai Chokevivat, until recently the vice chairman of Thailand's central ethics committee for human research.

Yet others in Thailand chafe at a system that allows Western researchers to present foreign test subjects with choices that provide less care and protection than those same researchers would be obliged to give subjects back in their own countries.

"It seems like every time this is the way things happen to Thailand," said Ratchanee Tunraka, a social worker with Siam Care in Bangkok, a charity that works with needy families, including some who participated in American research projects.

Why, she wondered aloud, are the studies brought to her country set up "to give someone nothing before we all can get a little something?"

A Race Against AZT For the past decade, many U.S. researchers working overseas have given test subjects care only as good as the best local care available.

Thailand's experience with this practice has sometimes left a bitter aftermath. Consider, say some Thai doctors, the choices made by Lt. Col. Merlin L. Robb of Maryland's Walter Reed Army Institute of Research.

In late 1994, Robb drafted a proposal for a study of mother-to-child HIV transmission in northern Thailand. He wanted to join with Thai doctors in the city of Lampang to measure HIV characteristics of a mother's blood and cervical fluid for clues about a child's risk of infection. Urgent answers were needed: 10 HIV-positive women a month delivered babies at Lampang Hospital.

From the start, internal memos show, Robb was racing other U.S. researchers vying for access to test subjects in Thailand and racing the march of the anti-viral agent azidothymidine, commonly known as AZT.

Robb had said from the outset that if AZT became available in the area, he would encourage his Thai collaborators to use it. But if AZT did not arrive before his research concluded, he said, it would make for better results -- because the drug would not cloud the natural passing of HIV from mother to child.

Robb had barely finished his research proposal before the ethical ground began to shift beneath him. A major study of pregnant, HIV-infected women in the United States and France showed AZT reduced newborn

infection rates. The 1994 results were so dramatic -- cutting infection rates by two-thirds -- that AZT became standard treatment in industrialized countries.

Robb's trial design called for no AZT for mothers or their infected babies. AZT was scarcely available in Thailand, and Robb argued to an Army ethics board that withholding AZT would not deprive women and their children because they had little chance of getting the drug anyway.

On the other hand, giving test volunteers AZT could muddy his research and could, he said, attract "patients from other provinces, consequently increasing the health care burden at [the experiment's hospital] beyond its capabilities."

Two Army ethics board members objected. "We should insist on the use of AZT," wrote Michael Mazaleski, a civilian member of the Army's Human Subjects Research Review Board.

The full panel approved Robb's research, and in 1996 Robb won a grant from a division of the National Institutes of Health that would total $1 million.

Writing to a colleague, Robb said he was "somewhat uncomfortable" with the decision making by bioethicists "since their deliberations seem often devoid of the larger view of advancing medical science for the public good as opposed to the individual."

Less than a year after he enrolled his first mother in the test, Robb learned AZT was making its way to Lampang. A Harvard team was giving AZT to all pregnant women in research it had launched in the area. Meanwhile, Thai health authorities said they planned a pilot study on AZT in local hospitals. With the local standard of care changing, Robb and his team revisited their decision not to use it.

Robb asked NIH in early 1997 if he could redirect $15,000 of his grant to buy AZT and provide it sooner than the Thai government project would. NIH declined, saying the change would require a new, lengthy review of his proposal. It suggested he collaborate with the Harvard team -- which also was NIH funded -- if he wanted quicker access to AZT.

Robb's team in Lampang did not want to "surrender the site" to Harvard, e-mail messages show, and told him they preferred to wait and get AZT from the Thai government project. In a recent interview, Robb said he never intended for his research to get in the way of women receiving AZT once it was widely available, but he said he also did not want to override his Thai team's decisions.

As a result, the mothers in Robb's study went without AZT for another three months, until July of 1997 when the Thai government project started. The 101 women who got no AZT gave birth to 22 infected infants.

More than four years after his research began, final results have yet to be compiled, but Robb remains convinced the work could eventually prove valuable in the design of an AIDS vaccine. "This was ethical research," he said, that will elucidate "benchmarks for vaccine development."

"It was a disgraceful, shameful study," countered Vallop Thaineua, director of the Ministry of Public Health's regional office in northern Thailand.

But like Robb, his local collaborators take pride in their work. "I do not feel bad about our work. I believe it will be useful," said Vilaiwan Gulgolgarn, a research team member who now treats some of the HIV-infected children born during the study.

"We were ethical," she said, "the drug was not here from the government, and until then we did not need to provide it."

Unequal Odds Robb's study was up and running in Lampang when researchers from VaxGen, Inc., a California-based biotechnology firm, arrived in Bangkok.

VaxGen had an AIDS vaccine under development in the United States, where 5,400 subjects, mostly homosexual men, had enlisted in tests. It wanted to add another 2,500 in Thailand, and to meet the need, it turned to drug addicts in Bangkok.

The Bangkok Municipal Authority arranged access to its 17 methadone clinics, where years of trust built up with counselors helped reassure heroin addicts about the experiment. "That's the reason so many agreed," said Kunyarat Maneesinthu, a psychologist at Bang Sue Clinic.

At the heart of negotiations between VaxGen and the Thai government was the question hanging over much of the research shifting to developing countries: How much did VaxGen owe participants or the host country?

VaxGen bargained tough. It risked losing Thai public support when it refused to pledge care for subjects who became HIV positive during the test. Thai health authorities finally stepped in and promised to provide the best local therapy -- which was years behind what an American could expect.

VaxGen also refused to guarantee that the vaccine, if proven effective, would be sold to Thais at a reduced price. VaxGen recognizes the "special situation we have with Thailand," company president Donald P. Francis said recently. "They bought in very early to this and we said we would work as hard as we can to reduce the price for them. But we can't give vaccine away and bankrupt the company."

VaxGen also rejected the Thai requests for profit-sharing or a manufacturing plant to be located in the country. A "gentleman's agreement" the company wrote in 1998 to Thai health officials, suggested that if the Thais helped with packaging the vaccine, VaxGen might be able to reduce the country's costs for the vaccine. But "we will have to wait to see what actually happens with the Bangkok study."

The deal seemed the best Thais could get, said Jon Ungphakorn, who reviewed the study and is now a member of the Thai senate. "We were making test subjects available and we were agreeable to that. But on the other hand, we did not have that much bargaining power. Our situation was desperate."

Inside Bangkok's drug clinics, VaxGen used methods that would have been novel in the U.S. to recruit and track volunteers, records and interviews show. The company joined in a clinic program that offered free rice to addicts who brought in five friends. It tracked addicts into jails if they were arrested during the experiment so that shots and blood tests could be administered.

The Thai experiment's structure contrasted with the U.S. tests. In each arm, some volunteers received real vaccine and some dummy medicine, a calculated risk since participants in both studies were at high risk of contracting the virus. But Thais in VaxGen's ongoing study have a one-in-two chance of getting the real medicine. American volunteers have a two-out-of-three chance.

The Thai and American tests were designed differently because "it was thought it might be a motivational factor for American gay groups to participate" if they had a better chance at getting a vaccine, explained John G.

Curd, VaxGen's senior vice president for medical affairs. "That may have been part of it," said Francis, adding that there was also a scientific reason involved. With U.S. infection rates so low, a larger pool of subjects receiving the vaccine meant researchers would reach enough people exposed to the virus. That way, researchers could determine more clearly if the vaccine was working.

Debate over designs of the trials was inconsequential to Thai addicts, who in interviews said they signed up for the test out of a mix of motives.

Wivat Chotchatmala, 35 and eight years an addict, said he volunteered "because I want the money" -- about $9 for each of 15 visits, about a day's pay for drivers of *tuk-tuks*, Bangkok's three-wheeled motorcycle taxis. But he also wanted to "do something useful for society and get a chance maybe to protect myself."

The vaccine volunteers "are swept up in the mood that they can do something for their country. That is a powerful and persuasive appeal for Thais," said Supatra Nakapew, director of the Centre for AIDS Rights in Bangkok.

VaxGen has invested $585,000 in equipment and facilities -- which will remain in Bangkok when the test is over. But VaxGen's principal Thai investigator, Kachit Choopanya, said his overriding hope is that the vaccine will work. "That is the benefit we want most."

Next fall, a VaxGen committee will examine early results from the American study arm. VaxGen says it will stop both branches of the experiment and seek FDA approval if the vaccine proves 30 percent effective -- a low threshold compared with other common vaccines.

If the drug is approved, VaxGen says, the Thais will immediately get one benefit akin to the U.S. side: All volunteers who received placebos will be vaccinated free.

Ethical Firestorm The "race to the bottom" is how some medical ethicists have described drug researchers' moves into developing countries. But public health researchers, including some from developing countries, denounce as "ethical imperialism" the notion that Western standards of care always must prevail.

"The easy thing to accuse [international drug testing] of is Yankee exploitation, of taking advantage of disadvantaged populations," said Robert H. Rubin, professor of health sciences and technology at Harvard Medical School and a clinical trial pioneer in the United States. "Frankly, that's nonsense.

"It has to be done right, and appropriately, [but] if you believe as fervently as I do that there is benefit to society . . . then all society should bear some of the burdens" of developing new drugs.

The opposing viewpoints clashed sharply this fall as the World Medical Association met to revise the 1964 Declaration of Helsinki, the statement of principles that has guided ethical decisions in drug experiments around the world. With representatives from 45 countries, including developing nations that have become hotbeds for drug research, the conference voted to clarify language on the use of placebos, making it unethical to use dummy medicines on some subjects in trials where proven treatments may be available. The declaration does not have the force of law in the United States, but it wields considerable moral clout.

Outrage over American experiments on pregnant women in Thailand and sub-Saharan Africa was a driving force behind the change.

Public and private researchers in the United States are still unsure how they can comply with the strong international mandate while trying to tackle the treatment and prevention of life-threatening disease. The National Bioethics Advisory Commission, a presidentially appointed panel that is drafting ethical guidelines, has struggled with both the placebo issue and questions about what researchers owe local populations once an experiment is completed.

"Clearly, this is an evolving issue," said Helene Gayle, director of the Centers for Disease Control and Prevention's National Center for HIV, STD and TB programs. "Through research, we cannot change the reality that there are inequities and there is poverty in the world. We should, as citizens of the world, attack that reality, but not through constraining research."

But ultimately, the West's anguished ethical debates occur far from the ordinary, struggling families swept along in the global drug testing boom.

So it was for Petprow Madornglang, recruited in November 1997 for an AZT test conducted by the CDC.

Madornglang, who lived in the rural province of Ayutthaya, was one of 397 HIV-infected pregnant women who signed up for the test at Bangkok's Rajavithi Hospital. Once a week until she gave birth, she made the two-hour trip, crowding into the back of a small truck, then transferring to a van that left only when it had a full load.

Under the study launched in 1996, half of the pregnant women in the experiment received AZT, but in a shorter course -- for fewer weeks and less frequent doses -- than was standard in the U.S. The Thai newborns would get no AZT, unlike American infants who had received AZT for six weeks after birth.

The CDC's decision to use a placebo for half of the Thai study's participants -- thus exposing some of their children to HIV, which presumably would have been prevented by AZT -- outraged medical ethicists in the United States.

"If you have a safe and effective treatment anywhere in the world for a life-threatening condition, from that point on you cannot ethically conduct a clinical trial that gives some people placebo," said LeRoy Walters, a Georgetown University bioethicist. Researchers had other options. A Harvard team was studying how different doses of AZT worked on the transmission rate, for example.

But dropping the dummy pill from the research, the CDC contended, would have required adding more test subjects to ensure statistical integrity, adding time to the launch of the study and muddling the comparison. The Thai central ethics committee agreed.

"We felt it was not only ethical, but it was essential to conduct" the study, said the CDC's Gayle.

The CDC study tracked Madornglang and the other mother-child pairs for 18 months, and in the end, reported that the short course of AZT could reduce transmission by half. The results helped shape national health policy in Thailand, which early this year pledged to provide the treatment free to pregnant women.

With only half a chance at help, Madornglang wound up with the worst half, said her sister and a Thai doctor. She got the placebo.

In Bangkok, Madornglang's family still replays the "what ifs."

Her sister, Anchalee Soithong, did not want her in the test. Soithong volunteered at the Thai Red Cross, which offered the equivalent of the American-style treatment. She also knew that another Bangkok hospital had a more modest AZT program. She tried to persuade, cajole, and berate her sister into listening on a night when they huddled together in a bedroom, whispering about the infection and the pregnancy, trying to hide the news from their mother.

"I didn't want her to take a chance with her baby," Soithong recalled. But Madornglang wouldn't change her plans.

Madornglang joined the research in November 1997 while showing symptoms of HIV, including fungus in her mouth and skin lesions, according to a summary of her case.

After seven months, researchers referred her for medical care for her HIV symptoms, giving her some antibiotics. Despite that, she withered. And when she returned 10 weeks later, she was not further investigated or treated, according to a summary of her case.

Madornglang died in October 1998. She was 28.

"Placebo or AZT? Which worked better? That was their question and she helped them get the answer," Soithong said. "My question was why did they not take better care of my sister?"

Madornglang left behind her son born in January 1998, one of the 37 infants born with HIV. She called him Kittisak, but nicknamed him "Ice," because it seemed soothing in such a hot climate. And "because it sounded American, like that singer," said Soithong.

The boy received AZT and other treatments as his health deteriorated.

Ice lived long enough to pull himself up along the edge of tables, but not long enough to learn how to walk. He died last December. He was 23 months old.