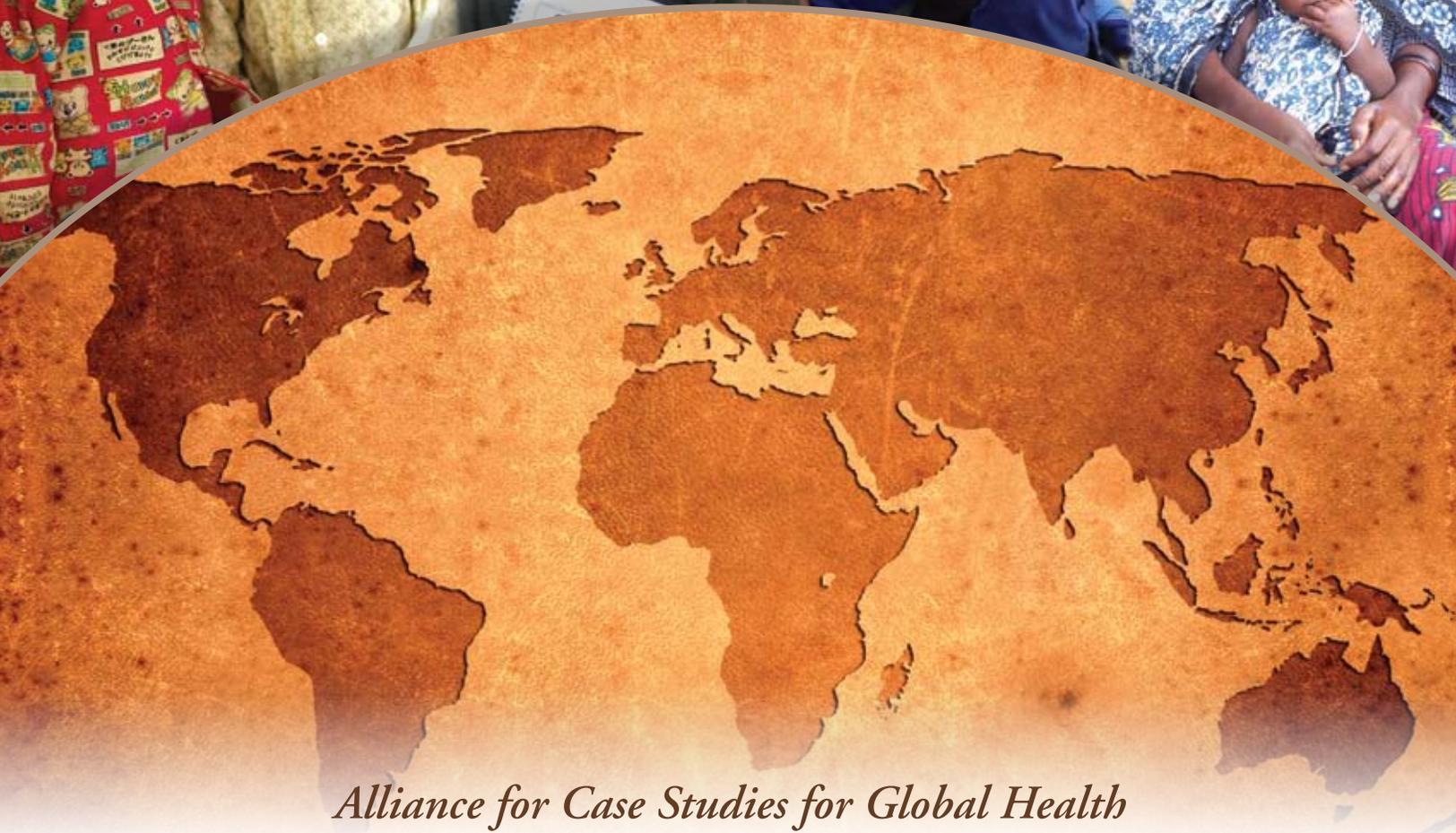


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Case Studies for Global Health

Case Studies for Global Health: Building relationships. Sharing knowledge.

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Methods and Acknowledgement

This publication is an initiative of the Alliance for Case Studies for Global Health, a collaboration of the Association of University Technology Managers (AUTM), the Bill & Melinda Gates Foundation, Global Health Progress, the International AIDS Vaccine Initiative (IAVI) and Tropical Disease Research (TDR). The alliance members conceived of this multisector case study initiative in December 2007. Over the following nine months, representatives from each organization shaped our vision of the scope and nature of this publication. We rested on the following objectives for the case studies:

- They would be solicited from a wide range of stakeholders within global health (e.g., private funders, multilateral organizations, academia, pharmaceutical and biotech companies, product development partnerships, and governments) and reflect current transactions and relationships.
- They would illustrate how people, organizations, companies and governments have worked together to try to solve a global health challenge. The wide range of potential topics would include the complexity of intellectual property, length and stage of product development, costs and nature of manufacturing, purchasers and markets, financing mechanisms, regulatory issues, capacity building, delivery mechanisms, and adoption hurdles.
- They would provide information on current practices and lessons learned in the course of conducting business and structuring partnerships.

We reached out to many universities, organizations, companies and governments to identify potential case studies. To capture as many diverse stories as possible, we published a call for case studies in various newsletters, journals and on Web sites during the fall of 2008, which generated considerable interest and a significant number of submissions.

In February 2009, we established a selection committee made up of representatives from the five Alliance members, along with a representative of BIO Ventures for Global Health and several global health experts from Africa and India. The members of the committee selected a total of 32 case studies based on their adherence to the core themes, framework and objectives of the initiative.

During the following months, the case studies were developed and written with the help of many individuals and organizations, including those involved in each partnership; this book would not have been possible without them taking the time to share their experiences, challenges and successes.

The result is the set of stories contained in this publication, which represent a wide range of stakeholders, activities and approaches. We would like to acknowledge the following organizations and individuals for their many hours of hard work and dedication.

Organizations Within the Alliance for Case Studies for Global Health

Association of University Technology Managers (AUTM) – Vicki Loise, Executive Director; Jon Soderstrom, Ph.D., Immediate Past President: AUTM is a global network of more than 3,500 technology transfer professionals who work in academic, research, government, legal and commercial settings. AUTM is dedicated to promoting and supporting technology transfer through education, advocacy, networking and communication.

Bill & Melinda Gates Foundation – Erik Iverson, Associate General Counsel, Global Health Program; Jennifer Haberman, Paralegal, Global Health Program: Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health and giving them the chance to lift themselves out of hunger and extreme poverty. In the United States, it seeks to ensure that all people — especially those with the fewest resources — have access to the opportunities they need to succeed in school and life.

Global Health Progress – Paul Antony, M.D., M.P.H., Executive Director (GHP) and Chief Medical Officer, Pharmaceutical Research and Manufacturers of America (PhRMA); Mark Grayson, Deputy Vice President, Communications & Public Affairs (PhRMA); Stephen Sobhani, Senior Director, International Alliance Development (PhRMA); Margaret Wu, Senior Associate (APCO Worldwide): The Global Health Progress initiative brings together research-based biopharmaceutical companies and global health leaders to improve health in the developing world. The initiative provides a platform for research-based biopharmaceutical companies, governments, public health leaders, universities, foundations, and other stakeholders to share experiences and best practices and to forge new partnerships.

International AIDS Vaccine Initiative (IAVI) – Labeeb Abboud, Senior Vice President & General Counsel: IAVI is an international not-for-profit organization whose mission is to ensure the development of safe, effective, accessible prophylactic AIDS vaccines for use throughout the world. IAVI is headquartered in the United States, with regional offices in Amsterdam, Delhi, Nairobi and Johannesburg, and operates in 25 countries. IAVI works in partnership with governments, civil society, academic institutions and industry in its research and development, advocacy and policy activities.

Special Programme for Research and Training in Tropical Diseases (TDR) – Solomon Nwaka, Leader, Drug Discovery for Infectious Tropical Diseases and Innovation for Product Development in Developing Countries: TDR is an independent global program of scientific collaboration that helps coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged. TDR is administered by the World Health Organization, and co-sponsored by the United Nations Children's Fund, the United Nations Development Programme, the World Bank and the World Health Organization.

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Foreword

“If you want to go fast, go alone.
If you want to go far, go together.”

(African proverb)

In recent decades there has been monumental progress in addressing the challenges of global health. More public and private money than ever is targeting the diseases of the poor. New drugs, vaccines and other tools are in development or in the field. Systems for delivering health care are improving. In 1960, 20 million children under age five needlessly died from preventable diseases. Today, that number is less than nine million. Much more needs to be done, of course. But without a doubt, nothing can be achieved without the partnerships and collaborations that are crucial to enacting meaningful and lasting change.

The stories presented in the *Case Studies for Global Health* provide an inside look at the ways in which partners have addressed the complex challenges of developing and delivering effective health care for the developing world. They illustrate the ways various stakeholders — private funders, world health agencies, academics, pharmaceutical and biotechnology companies, public-private partnerships, and governments — have come together for a common purpose. As these relationships are formed and disbanded, programs initiated and completed, and information gathered and assimilated, we can all benefit from the lessons learned.

We hope this publication will serve as a guide to the broad range of stakeholders who have voiced an interest in understanding how to efficiently build and manage technologies and partnerships. These case studies focus on the underlying relationships and transactions that drive each project. They assess the people and organizations required, how and when these relationships were formed, the respective roles of the participants, the hurdles in bringing them together, and the time and other resources required to make the project happen. Some are success stories. Some are not. Most are works in progress. But in every case, these are frank and honest assessments of what was learned along the way.

The case studies are divided into four categories — access to medicines and health services, discovery and development of new drugs and vaccines, health intervention and prevention programs, and health systems strengthening and capacity building. You will

read examples of how partnerships and collaborations accelerate efforts to fight well-known diseases such as HIV, tuberculosis and malaria, as well as lesser-known diseases such as dengue fever, hookworm and Japanese encephalitis. The examples provide lessons in how organizations can work together to build networks and capacity, localize training of medical personnel and foster novel research approaches.

In the process of collecting concrete examples of how global health problems can be addressed, some common themes emerged. For example, the success of a program can often be linked to traits such as early engagement of partners and policy-makers, open and frequent stakeholder communication and community empowerment. Yet most of the case studies do not fit neatly into one of the four categories. Each case begins by citing the lessons learned to underscore the fact that every situation presents its own set of challenges and that there is no single approach that will ensure success. As you read through these stories, you will see that the parties involved learned through trial and error and built upon previous successes and failures.

We would like to recognize the impressive efforts that have previously addressed the demand for case studies, including the Center for Global Development’s *Case Studies in Global Health: Millions Saved*, AUTM’s *Better World Report*, BIO Ventures for Global Health’s *Global Health Innovators: A Collection of Case Studies* and others. Our hope is that this publication complements these efforts by presenting the stories from a slightly different angle. We came together to achieve a common goal, which we feel is critically important to shaping the way we and our contemporaries construct programs to address global health issues in the future. Our collective effort created a publication that is broader in scope and more comprehensive and insightful than any of us could have produced on our own.

Most important, however, is the remarkable and critically important work of the governments, organizations, companies and individuals highlighted in this publication. The outcomes of their work, and their desire to collaborate and form partnerships, provide valuable lessons and insight. We hope our readers will discover useful approaches and tools for addressing the challenges of global health — and some inspiration along the way.

A Marriage of Divergent Interests: Partnership in the Making of the World's First Advance Market Commitment



Lessons Learned:

- *The heart of an Advance Market Commitment is that it is a multi-sector effort to build financing mechanisms as an incentive to facilitate vaccine development.*
- *Technical, financial and scientific issues associated with the AMC require the coordination of a wide range of subject matter experts.*
- *Being flexible and willing to revise your approach when new facts emerge or conditions change is critical.*
- *Being proactive is essential. Provide opportunities for continuous communication among all partners and stakeholders, identify those who can provide constructive suggestions and ensure they're heard by the policy-makers.*
- *Pricing is likely to be a key driver. Be reasonably certain that parties have consensus on timing and mechanisms for determining pricing.*



Enrolled midwife Belita M. Ngoma weighs and vaccinates baby with mother at Maternal Child Health unit in Kapiri Mposhi, Zambia.

Photo by Indrias Getachew

Vaccination remains the most cost-effective intervention available to modern medicine. It has arguably done more to improve public health than any measure except the provision of clean drinking water. Yet some two million children die each year from diseases for which vaccines already exist, and millions more lose their lives to infections against which vaccines could be developed, but never have been.

There are many reasons for this neglect. One is that the design and development of vaccines is, in some crucial ways, as much an industrial art as it is a science. Only a handful of companies have the know-how required to shepherd a candidate vaccine from its design stages through clinical assessment and regulatory review and onto the market. Further, because vaccines are biologics, their production is a relatively complicated and expensive affair. A single industrial-scale vaccine plant can cost several hundred million dollars to build, and its construction must often start three to four years before the vaccine has even won regulatory approval. It can, further, take a decade or more before the sizable investments made in developing and manufacturing vaccines generate the first

trickle of revenue. Given such high risks and steep upfront costs, manufacturers have long lacked any incentive to invest in vaccines tailored to meet the needs of developing countries, where few people could afford them.

This market failure was the focus of a report Italy's Minister of Economy and Finance Giulio Tremonti presented to his G7 counterparts on Dec. 2, 2005, in London. The Tremonti report identified six diseases for which vaccines ought to be developed and described how a financing mechanism known as the advance market commitment (AMC) might be used to enable their development. The AMC, a brainchild of researchers at the Center for Global Development, Washington D.C., creates an incentive for manufacturers to invest in vaccines for developing countries by guaranteeing them, for a defined period, a high price per dose for vaccines that meet specified criteria. That price, subsidized by donors supporting the AMC, alleviates some of the risk manufacturers must take as they expand production capacity. In exchange for this subsidy, the manufacturers agree to sell the vaccine at or below a preset lower price (known as the "tail price") after the donor funds that provided the initial subsidy have run out.



Health worker Elisee Sansa records information about women and their children at the Barumbu mother and child center in Kinshasa, Democratic Republic of the Congo.

Photo by Olivier Asselin

The G7 ministers endorsed the Tremonti report and convened an expert committee to decide which of six developing world diseases identified in the report ought to be the focus of a pilot vaccine AMC. Separate working groups were appointed to build a feasible technical, institutional and financial framework for the pilot AMC. The ministers also set in motion a widely inclusive consultation process to help inform its ultimate structure and vet it with all stakeholders. The World Bank, which had shepherded the idea through international summits and conferences since its arrival on the world stage, led these activities in conjunction with the GAVI Alliance. The latter has been chosen as the institution that would house the AMC secretariat and will contribute a vast portion of the funds for the purchase of vaccines. (See Table I for a list of the major partners.)

On Feb. 9, 2007, an AMC for a vaccine against pneumococcal disease — which kills 1.6 million people every year, mainly in developing countries — was launched with \$1.5 billion in funding from Italy, the United Kingdom, Canada, Russia, Norway and the Bill & Melinda Gates Foundation. Aside from testing the practicality of the AMC concept, this pilot is expected to save more than seven million lives by 2030 and to do so at a cost of \$33 per disability-adjusted life year, a third the accepted benchmark for health interventions in developing countries.

To qualify for the AMC, a candidate vaccine must target serotypes 1, 5 and 14 of *Streptococcus pneumoniae*, which are highly prevalent in Africa and Asia. It must also cover strains responsible for 60 percent or more of serious pneumococcal disease, last at least 24 months on the shelf and be devised for easy delivery via the existing health systems of developing countries. Companies that meet these criteria will be able to claim an initial price of \$7 per dose of their vaccine and a tail price of up to \$3.50, which represents a 95 percent discount on the price currently charged in industrialized countries for a similar existing vaccine. Their share of the AMC funds will be tied directly to the total number of doses they commit to deliver. (See sidebar.)

Over the past couple of years, the World Bank and GAVI Alliance have coordinated working groups and held a dizzying array of consultations with donor nations, developing countries, United Nations agencies, nongovernmental organizations (NGOs) and industry to shape the pilot AMC. These meetings helped establish everything from how the pneumococcal vaccine would be priced and paid for to the specific requirements it must meet to qualify for AMC support. This case study examines some of the issues that arose during the development of this pilot AMC — which became officially operational in mid-June 2009 — and seeks to identify lessons that might be learned from the manner in which they were addressed.

The Consultations

The tension between human need and corporate profit that gave birth to the idea of the AMC permeated every aspect of its subsequent development. It ran like a live wire through the meetings between government representatives and industry leaders that took place after G7 summit at Gleneagles, Scotland, where the idea of the AMC was initially fielded. And it animated the consultations GAVI and the World Bank team held with NGOs and industry. Given the controversy associated with any use of public funds to subsidize drug companies, it was clear that fundamental decisions about the AMC's ultimate structure would have to be arrived at through a transparent process that was demonstrably independent of political and industrial influence. The appointment of an independent consultant to draw up the general structure of the pilot AMC was a good idea, says Susan McAdams, director of multilateral and innovative financing at the World Bank, who was involved in the AMC from its earliest days.

It did not, however, protect the pilot program from criticism. Some NGOs wanted more access to information about things such as the cost of making vaccines, which are closely held secrets of the industry. Others wanted the AMC to somehow modify prevailing intellectual property law. Certain organizations saw no reason to give pharmaceutical companies public funds to do what they believed the companies ought to be doing anyway. As far as this camp was concerned, the very premise of the AMC was flawed. "Those who are ideologically opposed to market-based solutions will never accept that anything like the AMC is a good idea," says Tania Cernuschi, senior AMC manager at GAVI. "What we tried to do was to engage those NGOs that had made positive criticisms and proposals."

The AMC secretariat took care to brief such critics and see to it that their concerns were at least heard by the expert committees charged with writing the details of the AMC. Médecins Sans Frontières' (MSF), for instance, had serious concerns about how the AMC subsidy was structured. In its original form, the AMC would have permitted a single company to lay claim to the entire AMC purse. (That risk had not escaped the attention of critics in academia either.) So GAVI got MSF in touch with the Economic Expert Group (EEG), which had been appointed after the launch of the AMC to sort through pricing and design issues. MSF's concerns were incorporated into the report ultimately submitted by the EEG. Subsequently, rules governing how many vaccines a company can commit to supply under the AMC were modified in a way that make it impossible for any single firm to monopolize the entire \$1.5 billion fund.

This didn't exactly make MSF a champion of the AMC; it still had a list of fundamental criticisms of the scheme. But the

organization was pleased that its concerns had been heard. "It was very important to engage the MSF," says Cernuschi. "You have to be proactive, provide constant briefings to partners." Such interactions, she notes, help identify those who are interested in seeing a proposal succeed and have something of value to contribute to the problem.

Expert Advice

If transparency mattered in the stakeholder consultations, it was perhaps even more important to the credibility of the expert working groups and advisory committees. "Development aid, even a scientifically driven process like the AMC, is fundamentally political," observes David Fleming, who worked on the disease expert committee that first recommended the pneumococcal vaccine for the pilot and went on to chair the EEG and co-chair the implementation working group that penned the details of the AMC. He points out that a number of interest groups — advocates for malaria, TB, HIV — were competing intensely to have their vaccine of choice selected. Any of them might have been legitimately picked for the pilot

The way the decision to target pneumococcal disease was reached, Fleming says, illustrates a key strength of the processes by which the AMC was designed. The group convened for this purpose comprised experts in everything from epidemiology to the legal and economic aspects of vaccine manufacturing. Two-thirds of them came from developing countries. Their deliberations were conducted in a highly transparent manner. "If it had been some

How the Pilot Advance Market Commitment Works

- Manufacturers sign legally binding commitments to supply a certain quantity of vaccines for 10 years at a price no higher than \$3.50 per dose. The vaccine must meet the target product profile requirements of the AMC.
- In exchange, the manufacturers receive an additional payment that averages \$3.50 per dose for roughly 20 percent of the doses they supply.
- The subsidy gives manufacturers the incentive to invest in building manufacturing capacity dedicated to supplying the vaccine of interest to developing countries.
- The AMC price includes a copay, which is paid for by participating developing countries and GAVI.
- By ensuring the availability and accessibility of pneumococcal vaccines, the AMC could save 900,000 lives by 2015, and 7.7 million lives by 2030.

donor group making the decision in a political atmosphere,” says Fleming, “it would potentially have gone the same way. But then it would have been subjected to the criticism that political, rather than public health or scientific issues, were driving the decision.” That, he says, would almost certainly have bogged down the process, which was complicated enough as it was. The decision to delegate scientific, technical and operational decision-making to groups of independent experts, he believes, did a great deal to nip accusations of political bias in the bud.

But not everything went smoothly in the advisory process. The initial, high-level frame of how the AMC was to be constructed was, for instance, developed in advance of the EEG being convened. The group was basically told to “figure out the details,” says Fleming. “But when we sat down to figure out those details, we realized that some of the fundamental premises underlying the project’s initial design were not going to work for the AMC.” As designed, the AMC would allow the first company to market with a vaccine to claim the higher AMC price for its product, and to do so until the money ran out.

The whole point of the AMC, however, was that companies should be incented by the top-off provided by donor funds to build dedicated manufacturing capacity for the developing world. But the economic analysis conducted by the EEG revealed that, if you allowed the first company to make a vaccine to collect the full subsidy, it would in fact have no incentive to build dedicated manufacturing capacity. It wouldn’t need to take on the risk of building a large amount of dedicated capacity for the developing world. “So it turned out that the original, fundamental concept of how the reimbursement in the AMC was going to work actually was not going to work,” says Fleming.

Trouble was, though, that the original frame for the AMC is what had been sold politically to the donors. Changing the structure

now, the EEG was aware, could provoke protest. After some tough discussions within the group, says Fleming, the EEG decided that the AMC would nevertheless have to be modified to remove that potentially crippling risk. Though many of the experts in the group had been involved in devising the original scheme, Fleming notes, they did not balk at revising their initial plan. “In my government experience,” says Fleming, who was once deputy director at the U.S. Centers for Disease Control and Prevention, “it’s unusual that there’s that degree of flexibility built into a process — so that you can learn and evolve as you go.”

Not everyone agrees that this was necessarily an asset. The EEG, says McAdams, was charged with basically working out the details of the AMC: how recipient countries would pay their share (through the existing GAVI mechanism for vaccine co-payments), how the subsidy would be paid out and, most critically, what the tail price would be. “Instead of tackling the issues that had been laid out for them — filling in the critical blanks — the group basically went back to the drawing board and wanted to redesign the AMC,” says McAdams. “This was two-and-a-half years in. It was well-intended, and it did add concretely in some ways to the overall structure. But I don’t think it was actually necessary or that it added materially. There are others who would disagree with that, but it did cause an eight- or nine-month delay.”

This could have been prevented with the establishment of solid deadlines for all major steps of the process, says McAdams. Such deadlines are critically important, she believes, to prevent a sense of drift from taking hold in a project with as many moving parts as the AMC. “What really mattered about it going off the rails was not so much the substance of the AMC, which I think was moderately improved, but that the timing and the deadlines and, most importantly, the level of working attention went down the scale.”

Table I
Major Partners

Institution	Role
GAVI Alliance	Houses the AMC secretariat providing programmatic and administrative support to the initiative. It has overseen the development of the pilot AMC and will contribute substantially to the long-term funding for vaccine procurement.
World Bank	Has overseen the development of the AMC pilot. Its board voted in April 2009 to put the \$1.5 billion subsidy for the AMC on the balance sheet of its subsidiary International Bank for Reconstruction and Development.
World Health Organization	Set the technical criteria for the selected vaccine and will prequalify (for safety and quality) products bought through the AMC.
UNICEF	Will be the primary procurer and distributor of vaccines
Governments of Italy, the United Kingdom, Russia, Canada and Norway, and the Bill & Melinda Gates Foundation	Donated the \$1.5 billion in funds for the AMC

A Fair Price

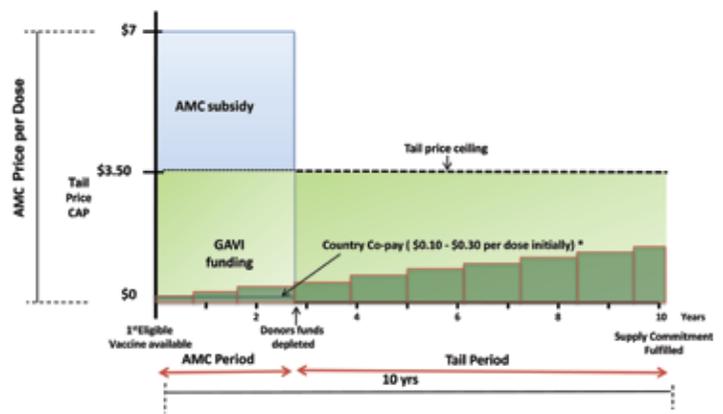
The groups working through the details of the pilot AMC had no shortage of information on their hands to guide them through their decision-making. But the one critical piece of knowledge they lacked, and had known all along they would lack, was the actual cost of manufacturing a vaccine. To the enduring irritation of many NGOs, the vaccine industry has long been jealously protective of this information. Meanwhile, outside analysts have doggedly sought to expose it.

The AMC designers stumbled into the middle of that game, says McAdams. They hired, over the course of the design process, three different consulting firms and a Nobel laureate economist to help them tease out the facts. Determining the costs of manufacturing mattered not just for the appeasement of several NGOs that suspected vaccine manufacturers would be overpaid by the AMC subsidy. It was also important for the retention of suppliers. Some sense of the cost of manufacturing is critical to setting the tail price of the vaccine at a credible level. “From a rational public policy perspective, and understanding what the externalities are about this,” says McAdams, “you should really be more worried about underpaying than overpaying. But [the AMC] is funded by sovereign donors, and they worry a whole lot more about overpaying than they do about underpaying.”

In setting the price, the AMC’s analysts did their research and crunched the numbers until they were reasonably confident that they had found a point that would incentivize suppliers, yet be affordable to procurers. But they can’t be certain that they’re not overpaying — not without having the facts about the cost of manufacturing in hand. “Industry,” as Fleming notes, “has every reason from a business perspective not to share that information.” This is likely to leave any AMC of the future guessing the right price as well. “Some sort of process that allows for the cost of the goods to be taken into account in a way that conceals that information from both competitors and the public is what needs to be developed,” says Fleming.

That isn’t likely to happen any time soon. But could the AMC concept be scaled up to address other market failures — say those associated with technology for climate change? McAdams says the questions to ask before that one are: what precisely is the market failure and is an

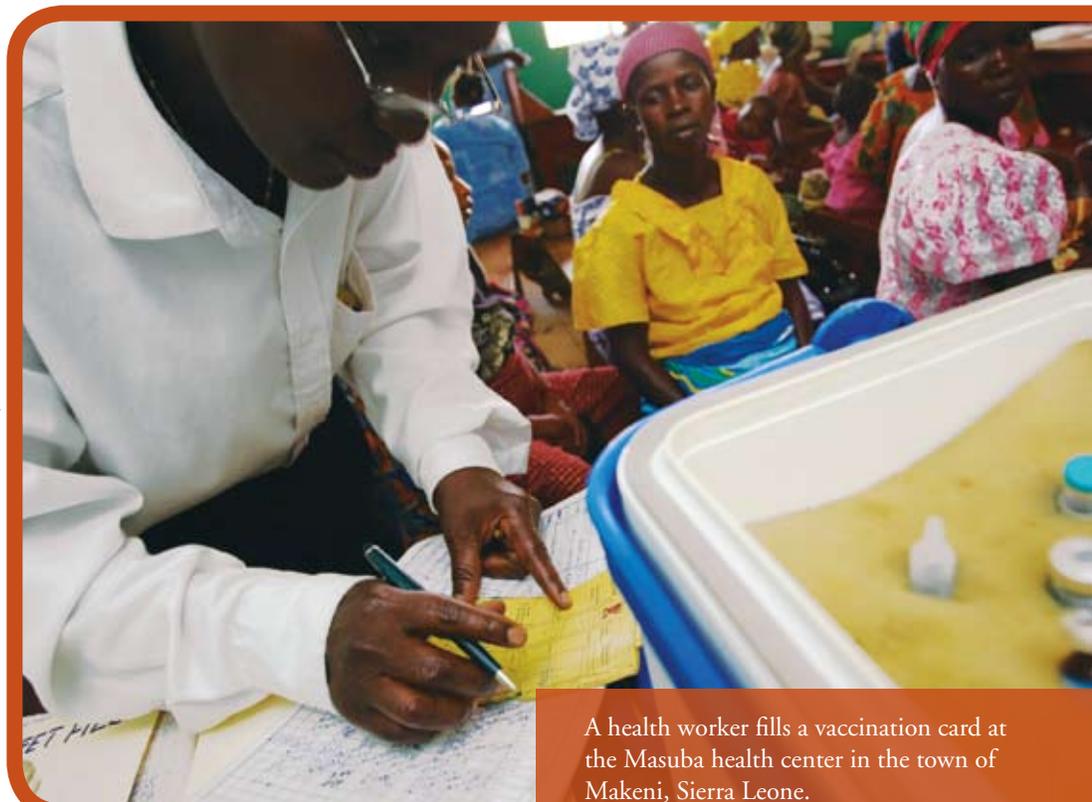
AMC Supply Agreement



This chart illustrates the AMC concept. Cofinancing levels will be in line with the applicable GAVI cofinancing policy.

AMC the right way to address it. Beyond that, the vaccine AMC isn’t necessarily the best way to tackle all infectious diseases either. “At the World Bank, we do not believe that an AMC will work for diseases like HIV/AIDS,” she says. “It’s so far out that you’d have to create a huge incentive without knowing if it will ever work out.” The AMC mechanism may well work to entice vaccine-makers into the business, says McAdams. “But the pricing is going to be tough.”

By Unmesh Kher



A health worker fills a vaccination card at the Masuba health center in the town of Makeni, Sierra Leone.

Photo by Olivier Asselin

Vaccine Vial Monitors: Small Labels With an Immense Impact



Lessons Learned:

- *Be thoughtful about making or demanding technical or manufacturing changes to a product to avoid making it impossible for the supplier to provide.*
- *Widespread support of an initiative like vaccine vial monitors can facilitate changes in global policy that allow more flexibility in the way that vaccines are used, resulting in further cost savings.*
- *A cost increase, even though minimal, can become a large obstacle to ensuring supply as procurers are often extremely price sensitive.*



Lab workers in the Bandung Bio Farma facility in Indonesia examine vials that have vaccine vial monitor technology incorporated into their labels.

Photo by Umit Kartoglu

Vaccines can be rendered useless by just a few degrees difference in temperature or by temperature changes over a prolonged amount of time, thus, making transporting these delicate solutions difficult. “All vaccines are sensitive to heat and some to freezing,” explains Umit Kartoglu, technical officer and scientist at the World Health Organization.

“The vaccines leave the production site in temperature-controlled trucks, are flown as cargo to the country’s capital for storage, then transported deeper into the country, stored again, and finally delivered to the location where they will be administered. Storage facilities often have sporadic electricity or no electricity at all,” explains Kartoglu. “Transport might be between islands or on dirt roads across rivers and swamps. Health workers carry the vaccine using trucks, motorbikes, boats, canoes, bicycles and, in many

cases, on foot. With all these steps, the journey might take a year, with the most challenging leg at the very end where the vaccinator struggles to reach populations dispersed by difficult geography, famine or war. The vaccine is at constant risk of damage.”

In the past, there was no way for health care providers in these tiny, rural villages to determine if the vials were unspoiled. Do they risk using costly but now worthless vaccines on patients and leave them vulnerable to the disease in the end? Or, do they toss expensive and perfectly good vaccine as a safeguard any time there is doubt of the vaccine’s viability? Neither alternative is acceptable where disease might advance quickly and resources to prevent or treat the illness are far too few.

A tiny sticker is now available that can warn health care providers if the vaccine has been exposed to heat and, therefore, spoiled. The label is small enough to fit on the vial label, the top of the vial



On the National Immunization Day for polio, two health care workers in Boboye village in Niger administer an oral vaccine to an infant being cradled in the arms of a woman.

Photo by Umit Kartoglu

cap or on the neck of the ampoule. A simple color change on this sticker indicates the viability of the vial's content with respect to heat exposure.

“Although developed as a heat-exposure indicator, vaccine vial monitors, often referred to as VVMs, also contribute significantly to the reduction of vaccine freezing,” says Kartoglu. “VVMs allow health workers to see the heat stability of vaccines and accept the fact that freezing is a greater danger than mild heat exposure.”

VVMs are a simple but effective system adapted from a similar labeling scheme used to guard refrigerated food during transport. The adaptation was an uncomplicated idea but a difficult reality. To date, only a single provider, Temptime, has perfected the technology to work on vaccines.

The tribulations did not end once the technology was mastered, however. It took more than two decades to turn this idea into a common practice in developing countries where adding even a penny's worth of difference to the price of vaccines was a burden they hesitated to bear. The price of the vial monitors was small, but still it was a price increase and, thus, a burden to overcome.

If it were not for the prolonged and consistent push by organizations like the World Health Organization (WHO), PATH, the United States Agency for International Development (USAID), the Global Alliance for Vaccines and Immunization (GAVI), United Nations Children's Fund (UNICEF), and the Centers for Disease Control and Prevention among others, the tiny label would have become stuck to a pricing hurdle. By adding the simple procurement specification requiring the VVMs, low-resource countries, where vaccines are the most at risk, now benefit from its simple but urgent warning.

Today, most vaccine suppliers comply with the UNICEF labeling requirement even though some organizations, such as the Pan American Health Organization (PAHO) still do not require it. PATH estimates that VVMs will enable workers to effectively manage vaccine supplies and replace more than 230 million doses of inactive vaccine and deliver 1.4 billion more doses in remote settings. UNICEF and WHO have estimated that the use of VVMs could save the global health community \$5 million per year if it's applied only to basic vaccines, and far upward of that figure if applied more broadly.

The Road to Certain Knowledge

Today's VVMs appear elementary in terms of design. A square of heat-sensitive material rests in the center of the circle-shaped label; it changes color after heat exposure. If the square becomes the same color as the outer circle, then the vaccine must be discarded because it is no longer effective. If the inner square is darker than the outer circle, the vaccine is long past the discard point. The color change is a continuous process and, thus, continues to indicate how quickly the vaccine should be used or even if it should be used at all. The combined effects of time and temperature cause the inner square of the vaccine vial monitor to darken gradually and irreversibly.

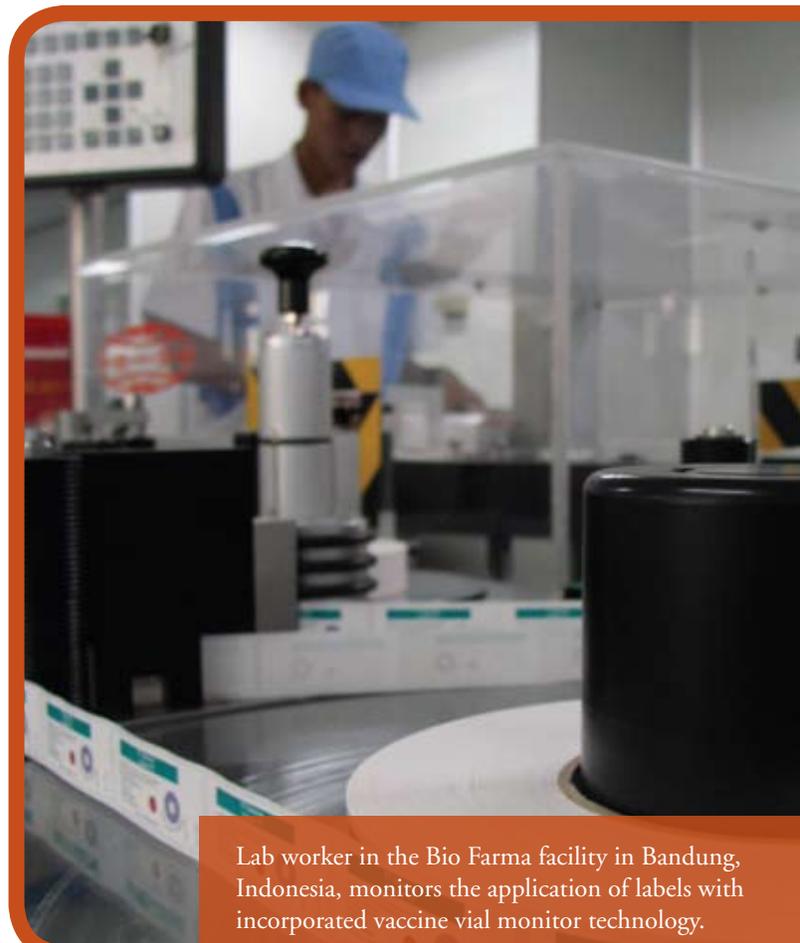
The simplicity of the label belies the difficulty in its development. The adaptation from existing cold chain (or temperature-controlled supply chain) labeling technologies used for refrigerated foods proved far more challenging than anticipated. Even Temptime, the sole producer of VVMs for vaccines today, abandoned earlier developmental attempts. PATH interceded and made a compelling humanitarian case for the product, and Temptime renewed its efforts until the product eventually was developed. To date, no other producer has been able to achieve the same success, although several are still trying.

PATH first tried to develop the technology on its own. The initial concept for a heat exposure indicator for vaccine vial use is attributable by all accounts to WHO officials in 1979. PATH responded by developing first generation prototypes for measles vaccine using a chemical licensed from Allied Corp. While this approach worked well with measles vaccine, it soon became apparent that it had limitations as the chemical was not responsive enough to work with the more heat-sensitive oral polio vaccine. The early work was funded by non-USAID sources, but USAID — through the HealthTech program — eventually became the most important financial supporter of VVM development and advancement. In the early 1990s, PATH/HealthTech worked with the Temptime Corp., then known as Lifelines Technology, to successfully modify its proprietary heat indicator technology for use with all vaccines of varying heat sensitivities. The resulting products became generically known as vaccine vial monitors. The Temptime brand is HEATmarker™, and it became commercially available in 1996.

Design field trials were conducted from 1990 to 1992 in Bangladesh, Bolivia, Cameroon, Indonesia, Kenya, Sierra Leone, Thailand and the United States. An additional detailed study on the impact of VVMs on measles vaccine discard rates due to heat exposure was conducted in Zimbabwe with the aid of the Ministry of Health. At the same time, WHO and PATH representatives met with eight U.N. vaccine suppliers to explore the feasibility of

integrating the labels with their products. Prototypes were then sent to vaccine suppliers for integration feedback. In 1993, Lifelines, now Temptime, developed the means to print VVMs directly onto vial labels, reducing manufacturer resistance to purchasing additional labeling equipment for a separate VVM label. PATH has assisted vaccine producers with VVM implementation throughout the program.

High on the list of acceptance problems early on was the fact that VVM is a paradigm-shifting technology available only from a single supplier, Temptime. The UNICEF Supply Division was not comfortable with the single-source issue, the subsequent deviation from procurement of commodity products and the added burden that the requirement placed on relationships with suppliers. PATH and WHO have continuously sought to develop other suppliers to address this issue. Technical assistance was provided to Albert Browne (U.K.), 3M (U.S.), Rexam/Bowater (U.K.), CCL Label (U.S.), and Sensitech (U.S.) but none have been successful in developing a price-competitive product that reaches performance requirements established by the U.N. agencies. PATH also assisted Temptime with obtaining low-cost loans to ensure production levels could meet global need.



Lab worker in the Bio Farma facility in Bandung, Indonesia, monitors the application of labels with incorporated vaccine vial monitor technology.

Photo by Umit Kartoglu



Two vaccination campaign workers give an injection to an indigenous inhabitant of a rural area in Peru.

Photo by Carib Nelson, provided by PATH

The principal patents owned by Temptime have expired, but since Temptime is able to meet global need easily enough and retains extensive knowledge and experience in manufacturing the VVMs. Technology transfer to other companies is not currently being pursued.

Strong support from several prominent agencies was necessary to continue to move the availability of VVMs forward. WHO was on board from the start. WHO staff members brought the need for this type of technology to PATH's attention, and PATH responded by identifying and testing appropriate solutions. PATH and WHO worked collaboratively on every aspect of VVM development and advancement.

UNICEF was kept apprised of the technology by WHO throughout the development process. Once the VVM technology was appropriately validated, WHO and UNICEF published a joint policy statement encouraging the inclusion of VVMs on vaccines. Eventually this policy translated into incorporation of VVMs into vaccine specifications for vaccines purchased by UNICEF.

WHO and the United Nations issued a joint statement in 1999 recommending VVM use on all vaccines, and the labels have since become a standard feature of all vaccines purchased through U.N. agencies. GAVI endorsement was a natural next step and was a straightforward process given the previous endorsement by WHO and UNICEF. In 2002, the GAVI board also stipulated that, from the beginning of 2004, all vaccines purchased through the vaccine fund must include VVMs. In the intervening years, PATH worked with Temptime, WHO and other collaborators to test, evaluate and advance the product.

A new advantage to using VVMs is beginning to surface. "VVM shapes the future of cold chain today, a future in which dependency on the cold chain is removed," says Kartoglu. "Today, VVM is seen as a catalyst for much-needed changes in strategies of vaccine distribution via the cold chain. VVM allows immunization programs to exploit the stability of each vaccine to the greatest possible extent, minimize distribution costs and increase flexibility in the handling of vaccines in the field, thus helping to make operations more effective."

The Struggle for Consistent VVM Use

Even with the advances in VVM technology and the spread of advantages the technology seems to present, consistent use of the product has been difficult to ensure.

While VVMs are increasingly supplied on vaccines purchased for the international market through UNICEF, they are not yet available on many of the vaccines produced in developing countries for domestic markets, the exceptions being India, Indonesia and Pakistan.

Vaccine procurement for developing and emerging countries is becoming increasingly decentralized, meaning that a variety of purchasers must include VVMs in their tender specifications to ensure consistent availability to immunization programs. In 2007, WHO and UNICEF released a policy statement encouraging member states, donors and nongovernmental organizations procuring vaccines to include VVMs in their specifications. Continued work to strengthen procurement at the country level, e.g., through interagency coordinating committees, will be necessary to ensure vaccine quality and availability of vaccines with VVMs.

Although PAHO supported a number of field trials with early VVM prototypes, it has never required VVMs on products purchased through the PAHO revolving fund, citing lack of cold chain difficulties in its region and unwillingness of consumers or purchasers to pay the slight price increases for products with VVMs. Vaccine suppliers complained that they had to supply vaccine with VVMs for UNICEF and without for PAHO, but eventually most complied with the UNICEF requirement.

One repeated difficulty has been the inability of the UNICEF supply system to consistently send the same brands of vaccines to countries or to notify WHO with regard to which countries would receive vaccines with VVMs. WHO was, therefore, unable to target early training efforts to countries that would definitely receive the VVMs. For many years, countries received supplies of vaccines both with

and without VVMs and, therefore, could not rely on VVM use as a routine management tool. This situation is improving as more vaccine suppliers have integrated VVMs into their products.

Immense Impact

Despite these difficulties and challenges, the overall impact of VVMs has been considered a global success. Future vaccine storage and transport will likely rely even more heavily on VVMs as the existing cold chains become constrained by the introduction of many new vaccines. VVMs could enable the removal of some heat-stable vaccines to higher temperature storage areas to make room for more heat-sensitive vaccines in refrigerators. The labels also have a proven history of enabling outreach to difficult areas and can continue in this role with new vaccines, such as conjugate meningococcal A vaccine.

The Optimize project is a joint WHO/PATH project focused on developing the strategies for the future of immunization logistics. Project Optimize is working to further improve the availability and utilization of the VVM as a vaccine management tool within countries.

By Pam Baker



Immunization session in Uganda

Photo provided by PATH

Growing Network Extends HIV Treatment to Children in Developing Countries



Lessons Learned:

- *Close cooperation between local governments and foreign organizations is essential for successfully delivering medical services in resource-constrained settings.*
- *Private and public donations of time, money and products — including those from pharmaceutical companies — are a critical component of launching and maintaining a global health effort.*
- *Training local health care personnel to meet international standards in specialized care is key to ensuring sustainability of the health program.*
- *The success of pediatric HIV programs leads to added challenges in sustaining long-term treatment as the patients mature.*



Mark Kline, M.D., and a group of physicians and nurses examine children in the outpatient clinic in Constanta, Romania, in 1997.

Photo by Smiley N. Pool

In the late 1990s, the new effective HIV regimens remained largely unavailable in resource-poor countries. Global AIDS deaths among children under 15 amounted to almost 300,000 in 1999, and the number of newborns acquiring HIV in the same year exceeded 400,000. High-income countries contributed a miniscule amount to those figures because of their ability to administer antiretroviral therapy (ART).

Mark Kline, in 1995, was savoring his success in treating HIV at Houston's Texas Children's Hospital. Kline, a professor of pediatrics at Baylor College of Medicine, was pulled out of his complacency by a group of visiting Romanian doctors. While Kline talked to them about pediatric HIV care at the Children's Hospital, his guests described the unique HIV problem in Romania. Some 10,000 neglected Romanian children raised in orphanages had contracted HIV due to hospitals' use of blood microtransfusions to "fortify" their health. Not only was this practice medically unfounded, but the transfused blood was unsterilized and the reused syringes unsterilized.

These children received little treatment, and the Romanian doctors were desperate. Kline returned the Romanians' visit in February 1996. "I thought I had seen it all before," Kline says now, "but I was not prepared for this. There were hundreds of stunted, wasted children with horrible open lesions. The kids had been warehoused in the AIDS ward and left to die. After two weeks in Romania, I thought, 'My conscience can't allow me to walk away.' I developed the outline for an international pediatric program on the plane home."

Kline started with a small amount of seed money but gradually built a public-private partnership that includes pharmaceutical company foundations, the United States and other governments, and international donors. The Baylor International Pediatric AIDS Initiative (BIPAI) now extends from Romania to nine countries in Africa (see map). As of 2009, it treats 30,000 patients. In developing this extensive network, BIPAI created an operational and financial model for bringing HIV care to resource-poor areas, something long considered impossible.

In the Beginning: Constanta, Romania

Kline's initial visit centered on the Black Sea port city of Constanta. He was the guest of one of the local pediatricians, Rodica Matusa. The city was the focal point of Romania's epidemic. At that point about 600 Constanta children had died of AIDS and another 600 were known to be HIV-positive. "We began a small program to examine the children and catalog their problems," Kline recalls. "We treated their tuberculosis and diarrhea, gave nutritional supplements and started training medical personnel. We saw a modest improvement in health."

Clearly more was needed. Matusa convinced her institution, the Constanta Municipal Hospital (since renamed the Infectious Diseases Hospital Constanta), to donate a nearby abandoned orphanage. Kline was able to secure initial renovation funding from a Houston-based religious order, the Sisters of Charity of the Incarnate Word. In addition, Abbott, the makers of HIV test kits and the popular HIV protease inhibitor Kaletra®, commenced its Step Forward program in 2000. Step Forward (managed by the Abbott Fund, the company's philanthropic arm) focused on orphaned and vulnerable children affected by the HIV epidemic. Its first grant went to create the Romanian-American Children's Center in Constanta, which opened in April 2001 with a Baylor and Romanian staff providing comprehensive medical and psychosocial services. For specialized HIV care, the center partnered with the government's Infectious Diseases Hospital, whose providers Baylor helped train.

Summarizing Abbott's early interest in the Romania-Baylor Project, Abbott Fund Vice-President Jeff Richardson says, "We heard from several people about Baylor's outstanding reputation in pediatric AIDS. Kline was one of our consultants when developing the Step Forward program. We were impressed not only with his proposed care and treatment model in Romania, but also with his promise that Baylor would replicate this model in Africa."

A steady source of antiretroviral drugs became available at the center in November 2001 when Abbott provided the Constanta patients with a lifetime no-cost supply of Kaletra. Kline was able to secure a stable supply of supporting nucleoside analogs through a Bristol-Myers Squibb donation. Later on, a grant from the Global Fund for AIDS, Malaria and TB allowed the Romanian government to become a reliable ART supplier. *(At publication time, however, recession-induced budget cuts have created a looming shortfall in ART availability.)*

Abbott also entered into an open-ended commitment to fund the clinic's operating costs. With the clinic's sustainability and access to drugs assured, annual mortality among the Constanta patients on ART progressively declined from 13 percent to 1 percent.



Sites of BIPAI's Clinical Centers of Excellence with opening dates (UC = under construction as of August 2009). Note that treatment programs generally began in local public hospitals with which the centers became associated upon opening.

Modified from: World Outline Map (no date). St. Catharines, Ontario: Brock University Map Library. (Accessed Aug. 15, 2009).

Aging patient population: The increased survival meant that the center was faced with a raft of new psychosocial issues. Ana-Maria Schweitzer is a Romanian psychologist who started working with the Baylor team in 1999 when all of the clients were under 18 years of age. She has since become the center's director, and now almost all of the clients are young adults. Schweitzer says, "Before, the priority was to ensure survival. Now the daily needs are covered, including uninterrupted drug supply. The new priorities include informed decisions on pregnancy or becoming parents. Out of our original population, we now have 50 couples with children up to four years old." The center provides its own obstetrics-gynecology and family planning specialists and social workers to provide care and counseling on the full range of family planning options plus preventing mother-to-child HIV transmission (PMTCT). So far, there have been no detected HIV transmissions to newborns.

A related issue is safe sex — counseling both the HIV-positive patients and their partners on preventing transmission, of which there have been suspected cases. Transmission as well as disease risk would decrease if everyone adhered scrupulously to their ART dosing schedules, but Schweitzer terms adherence "an everyday

struggle” for adolescents. The center’s adherence support efforts include focus groups, counseling and home visits.

The biggest new challenge is helping HIV-positive young adults to become productive members of society. Says Schweitzer, “There was a lack of education: Nobody expected these kids to live, so many didn’t go to school. Those who did faced considerable stigma. So we help find jobs by acting as a buffer between our patients, job trainers and employers. We have special connections with employers that we have educated on HIV.”

Collaboration with government and international donors: The Constanta Center has been fortunate that the Infectious Diseases Hospital continues to partner with it as part of the national AIDS program. The increasingly capable hospital staff is in charge of ART treatment for the center’s clientele as well as for the rest of the local HIV population. This center, meanwhile, transformed itself in December 2007 into the Romanian Clinical Center of Excellence. It now welcomes all of Constanta’s 840 persons with HIV, adults as well as children.

As the center’s primary donor, the Abbott Fund regularly consults about the center’s accomplishments and further needs. It supported the expansion of social services while the government oversees HIV treatment. This pattern of tight cooperation with the local medical establishment and with funders became basic to BIPAI’s expansion to African locales.

Thinking Large: Botswana

U.S. pharmaceutical company Bristol-Myers Squibb (BMS) commenced its \$150 million Secure the Future program in 1999 through the company foundation, just as the Constanta center was taking shape. Secure the Future was focused on southern Africa from the start. The BMS Foundation had worked previously with Mark Kline on the Romania clinic, to which it gave small cash contributions and drugs, and on training Mexican pediatricians. When launching Secure the Future, it immediately invited him to put together a new project based on the Romanian experience.

Collaboration with government and international donors: Far to the south of Constanta lies Gaborone, the capital of Botswana. Botswana has benefited from remarkable economic growth rates



Baylor International Pediatric AIDS Corps (PAC) physician, Kebba Jobarteh, M.D., exams a child at the Baylor College of Medicine Abbott Fund Children’s Centre of Excellence in Malawi.

Photo by Smiley N. Pool



PAC Drs. Kebba Jobarthe, Adrian Hazbun and John Midturi, discussing a patient while doing rounds at Kamuzu Hospital in Lilongwe, Malawi.

Photo by Smiley N. Pool

since independence and now has a per capita gross domestic product slightly higher than Romania's. But with a quarter of its adult population HIV-positive, Botswana has a far higher HIV rate. Botswana's government was also very supportive of bringing HIV treatment to its citizens. Its president, Festus Mogae, became personally involved in expanding treatment availability. A place like Botswana would naturally command Mark Kline's interest.

Arguably, the government's biggest contribution to BIPAI was Gabriel Anabwani, the chair of pediatrics at Gaborone's health care centerpiece, Princess Marina Hospital. Looking back, Anabwani says, "We were so frustrated to helplessly watch children die in our hands when the treatments were out there." He met Kline at a September 1999 BMS Foundation meeting. Kline visited Princess Marina Hospital, and the two put together a program of exchanges, training Botswana doctors in HIV treatment and U.S. doctors in opportunistic infections.

When Anabwani came to Houston for a month, he was impressed by how healthy the pediatric HIV patients were. They were living the lives of normal children. He wanted to show that African children could have a similar experience if ART were available.

Secure the Future funded the initial Botswana-Baylor effort in this regard, which effectively became a 200-child pilot ART program. The research team worked out of a small trailer behind Princess Marina Hospital.

As the Botswana government prepared to introduce ART throughout the country, Kline and Anabwani floated the idea of a separate pediatric HIV clinic. With the president's blessing, the Ministry of Health signed a memorandum of agreement to work with the project's treatment, training and research activities. The agreement committed the government to providing antiretroviral drugs as well as land for the clinic on the Princess Marina grounds. Kline convinced the president of Bristol-Myers Squibb, Kenneth Weg, to have Secure the Future grant \$6 million for the center's construction and first five years of operation. Additional funding came from the U.S. National Institutes of Health and Centers for Disease Control and Prevention.

"BMS agreed reluctantly," Anabwani recalls. "Nobody treated HIV then; they only did prevention. Mark and I agreed that if the center failed, it would be fatal to attempts to treat children in Africa. We had a huge responsibility."

Fortunately, the Botswana-Baylor Children's Clinical Center of Excellence was a great success from the time it commenced operations in June 2003. BMS Foundation President John Damonti says, "It is the most beautiful building at the hospital. There was fear going in that parents would not bring their children to an HIV facility given the disease's stigma. But they had 1,400 children on ART in the first year and 6,000 patients in the first two years. The center showed that the model works not just for training but also for catalyzing treatment and care." Most critically, annual mortality among the patients fell from 4.7 percent in 2003 to 0.3 percent three years later.

Addressing the shortage of skilled personnel: Training other doctors is an essential part of the center's program. "We have become a very valuable partner of the Ministry of Health," says Anabwani. We provide all the training in HIV care for the whole country. We also sit on the health ministry's key children's health committee." An international training program sends center doctors to other African countries for two weeks to one month.

Aging patient population: In 2009, the center had about 2,100 pediatric patients plus 260 families in its family care center. Botswana's PMTCT program has proved highly effective, with transmission reduced to levels comparable to those in developed countries. As in Romania, the pediatric patient population is aging rapidly. "In three to five years, the majority will be adolescents," Anabwani estimates. "We are advocating with the government, NGOs [nongovernmental organizations] and funders to sensitize them to teens' needs." In Botswana, too, ensuring adherence to dosing schedules is a big issue. Safe sex is another looming problem. One advantage over Romania is that patients' family structures are largely intact — and struggling with HIV together. Orphans are usually under the care of surviving family members.

A major effort has been made to establish teen clubs and an annual vacation camp. Adolescents also are given more frequent clinic appointments with doctors specifically interested in adolescent care. "Our efforts need more development to be effective," notes Anabwani. One of the remaining hurdles is transferring maturing patients to adult care. There are plans to ease the transition by bringing adult doctors to the pediatric clinic for extended periods.

New Frontiers

The BMS Foundation was so pleased with the Botswana experience that it moved to fund construction of six other clinics. The second Clinical Center of Excellence was located 300 miles (500 km) farther south, in Lesotho's capital, Maseru. Lesotho has a population similar in size to Botswana, and its HIV prevalence is about the same, too. But Lesotho is considerably smaller in size and its economy much poorer.

Collaboration with government and international donors: The Children's Clinical Center of Excellence in Lesotho commenced operations in December 2005 under a Memorandum of Agreement with the Lesotho government. There was only one pediatrician in all of Lesotho before the Center of Excellence opened. BIPAI brought in 10 doctors from the United States to provide sufficient pediatric care capacity. The government is paying for ART drugs and operating expenses with a grant from the Global Fund. UNICEF and private donors also underwrite various aspects of the operation. As of 2009, the center had 2,300 active patients, half receiving ART. Some 600 of the patients were adult family members of the pediatric patients.

To alleviate Lesotho's shortage of HIV care facilities, the Center of Excellence is constructing 10 satellite clinics outside Maseru to serve children and their families. The Lesotho government is providing the land and supporting the operating costs. Here too, the BMS Foundation is paying for construction while BIPAI will supply the staff.



Mark Kline, M.D., examines a patient at the Baylor College of Medicine Bristol-Myers Squibb Children's Center of Excellence in Lesotho.

Photo by Smiley N. Pool

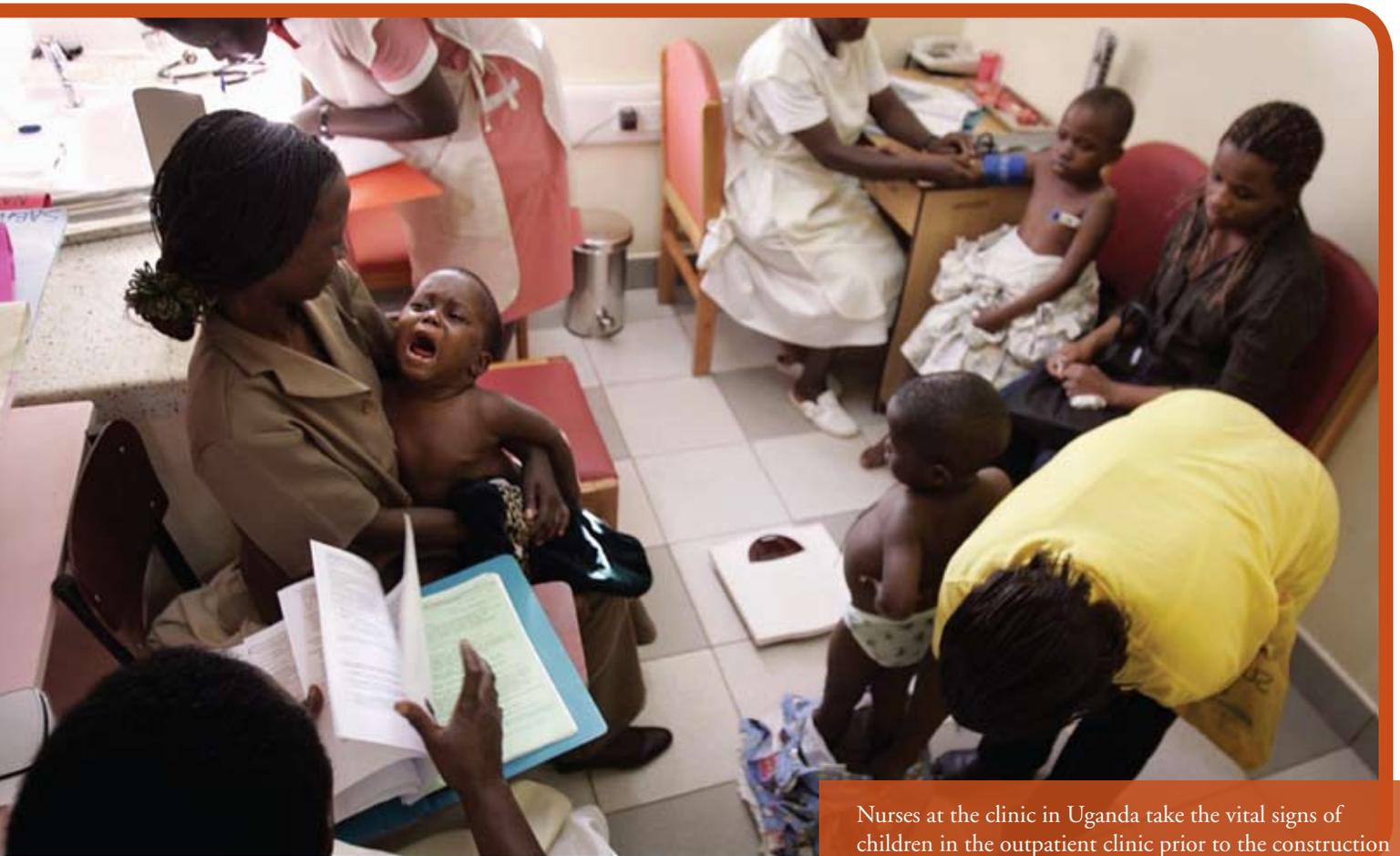
Further expansion: The BIPAI network continues to expand elsewhere. It opened a Center of Excellence in Swaziland in February 2006 and in Malawi in November of the same year. In October 2008, BIPAI opened a center in Kampala, Uganda, the culmination of a hospital-based program that began in 2002. The Uganda center cares for 4,000 pediatric patients with 7,000 more receiving treatment at affiliated clinics in Kampala and around the country. As of 2009, Centers of Excellence were under construction in Burkina Faso, Kenya and two Tanzanian locations. Swaziland's center is building two satellite facilities, which are also planned for Tanzania.

The BMS Foundation paid for constructing all but two of these sites, with international donors underwriting operational costs (principally the U.S. President's Emergency Plan for AIDS Relief and the Global Fund). The Abbott Fund supplied the funds for building the Malawi center and largely supports its continued operation. It is also financing construction of one of the Tanzania clinics.

Addressing the shortage of skilled personnel: A shortage of doctors has proved to be a universal problem. "We found that it was easier to build centers than to staff them," says Damonti. BIPAI announced in 2005 that it was organizing the Pediatric AIDS Corps, which Damonti's BMS Foundation agreed to fund for five years. The program supports 50 or 60 doctors from the United States each year at the BIPAI clinics and at remote sites. The doctors participate in the centers' care and training efforts for 12 to 36 months each. The Pediatric AIDS Corps is considered an interim measure until more African doctors are qualified in HIV care.

Keeping it all Together

In August 2006, BIPAI reported that it had less than 10,000 active patients; it reported an active caseload of more than 39,000 in October 2009. Kline has visions of eventually caring for 100,000 children with HIV — half the infected pediatric population in the countries with BIPAI clinics. The challenge will be to serve such a large patient body in a sustainable, well-organized fashion.



Nurses at the clinic in Uganda take the vital signs of children in the outpatient clinic prior to the construction of the Baylor College of Medicine Bristol-Myers Squibb Children's Centre of Excellence there.

Photo by Smiley N. Pool

A major effort to ensure continuity is BIPAI's Children's Clinical Centers of Excellence Network. Supported entirely by the Abbott Fund, this network meets several times a year, bringing together a large proportion of the far-flung clinic staff. It plays a critical role in integrating their activities. In addition, Abbott and BMS see the meetings as another means to informally coordinate their activities with the network and each other — beyond these donors' frequent site visits and personal communications.

The network also provides Abbott- and NIH-funded fellowships for study at the Baylor College of Medicine. The fellowships supplement the centers' many in-country educational courses, and they are an effort to establish native leadership to oversee continued HIV care.

Yet troubles loom on the horizon. For example, the Pediatric AIDS Corps at present fills in the doctor gap, but the \$22 million BMS grant that supports it ends in 2011. Either another funder will have to step in, or BIPAI will have to rely on the local doctors it has trained at that point. And where will the funds come for hiring more African doctors, whose expertise is also needed by nearby health care institutions?

One of BIPAI's major strengths has been its strong cooperation with the national governments where it has operations. "We consider ourselves an extension of the national government HIV programs," says Kline. "Our centers are kind of hybrids — they're international but they have one foot in the Ministry of Health." Kline believes that active government cooperation is critical. The governments cut through the ever-present red tape so that the centers can operate freely. They also support a substantial part of the centers' operating expenses in several locations. If motivated, they might help pick up the tab at other locations that lose grant money.

It would, therefore, be a bad idea to hire doctors away from existing institutions. BIPAI has agreed to avoid that in every country in which it operates. It refrains from economic competition by paying at the local scale. But the centers of excellence offer other advantages.



Baylor International Pediatric AIDS Corps physician, Kara DuBray, M.D., at the Queen Elizabeth II Hospital examines a patient in Lesotho.

Photo by Smiley N. Pool

Richardson notes, "Baylor is providing well-operated facilities that are attracting doctors back to their native countries or inducing local medical school students to stay. I hear from doctors and nurses that they want the tools to get the job done, and that this is at least as important as salary." BIPAI endeavors to meet the demand for a quality professional environment through its training programs, lab facilities and computer technology.

In any case, Kline foresees a period of consolidation. No new clinics are under consideration. He says, "Our primary thrust will be to realize the centers' full potential through extending pediatric and family care, professional development, satellite facilities and electronic health records. We are not growing the number of centers but concentrating on delivering the highest quality care and supporting the local health system."

By David Gildden

Saving Uzbek Hearts: A Program for Best Practices in Controlling Hyperlipidemia



Lessons Learned:

- *Design your health program in response to a locally identified need.*
- *An influential in-country champion will be an asset to your program.*
- *A chronic disease program must have a strong monitoring component.*
- *Make sure you are cognizant of the resource constraints of participating organizations.*
- *Build capacity to ensure your program's sustainability.*



A nurse records disbursement of simvastatin at the Cardiology Center in Navoi.

Photo by Jim O'Brien

To say cardiovascular disease is a problem in Uzbekistan would be something of an understatement. It is, in fact, epidemic. According to the World Health Organization (WHO), more than 56 percent of all deaths in the former Soviet central Asian republic are caused by this silent yet efficient killer. Many of them are premature, the likely consequence of multiple risk factors, such as heredity, tobacco use, physical inactivity, and untreated hypertension and high blood cholesterol. It has long been clear to many Uzbek physicians that preventive interventions are urgently needed to diffuse what is clearly a ballooning health care crisis.

In 2006, Alexander Shek, the chief cardiologist at the Republic Cardiology Center in Tashkent, met with AmeriCares and Soglom

Avlod Uchun Foundation, two organizations that were working closely with the hospital on a variety of projects. AmeriCares is a U.S.-based humanitarian aid organization that specializes in medical commodity assistance, and Soglom is an Uzbek nongovernmental organization focused on health care. He asked if AmeriCares could help him address the widespread problem of hyperlipidemia (high cholesterol) in Uzbekistan as part of its aid efforts in the country. In particular, Shek wondered whether it could regularly donate the cholesterol-lowering drugs known as statins to cardiology centers to help physicians treat hyperlipidemic patients.

A series of conversations about program design and implementation culminated in June 2007 with the launch of the Central Asian Cardiovascular Disease Initiative (CACDI). To help fulfill the request for hyperlipidemia treatments for



A nurse takes blood pressure and pulse during patient visit.

Photo by Jim O'Brien

indigent patients, AmeriCares reached out to Merck & Co. and Merck/Schering-Plough Pharmaceuticals, which agreed to donate the drugs, Zocor, Vytorin and Zetia. “Our program had three primary goals,” says Ella Gudwin, director of global partnership development at AmeriCares. “One was the treatment of patients who lacked the means to pay for treatment. Another was to develop the expertise among physicians in the treatment and monitoring of cardiovascular diseases. And the third point of emphasis was patient and family education.”

The fulfillment of the last two objectives, it was hoped, would give CACDI an impact that reached beyond its small scale. Owing to the cost and spotty availability of statins in Uzbekistan, relatively few physicians had developed a working knowledge in the use of pharmaceutical agents for hyperlipidemia treatment. That, however, was slated to change. Three major cholesterol control drugs — Merck’s Zocor (simvastatin) and Mevacor (lovastatin), and Bristol-Myers Squibb’s Pravachol (pravastatin) — went off patent in 2006, and their prices had begun to drop. In 2007 the WHO put simvastatin on its Model List of Essential Medicines, which many ministries of health use as a guiding document for filling national formularies.

Setting Up

CACDI is built around statin therapies, which are regarded as generally safe and effective medicines. Patients in the program are treated with simvastatin, ezetimibe — a drug that lowers cholesterol by a different mechanism of action than do the statins — or a combination of the two. Roughly 420 patients are enrolled in the initiative at any given time. They are treated by heart specialists at one of seven medical centers across Uzbekistan, though most visit the Republic Cardiology Centre in Tashkent. Enrollment is not randomized. Indeed, it has been engineered to bias the outcome positively. To be selected for the program, hyperlipidemic patients must be of sufficiently modest means to find treatment financially challenging. But, just as importantly, they must demonstrate that they and their spouses or other family members are committed to their participation. This is because the program requires lifestyle and diet changes in which family are likely to play a leading role (women, for instance, cook the meals in most traditional Uzbek households).

As a component of program monitoring, physicians must report total cholesterol levels. “We wanted the total cholesterol measurement to be used as reliable proxy for therapeutic responses to the antilipidemic therapy,” Gudwin explains. In line with best practices, physicians also take measurements of the LDL cholesterol (“bad” cholesterol) HDL cholesterol (“good” cholesterol) and triglyceride levels of patients. But these measures are only used by the physicians to monitor patients and inform them of their progress. They are not reported to the pharmaceutical donors.

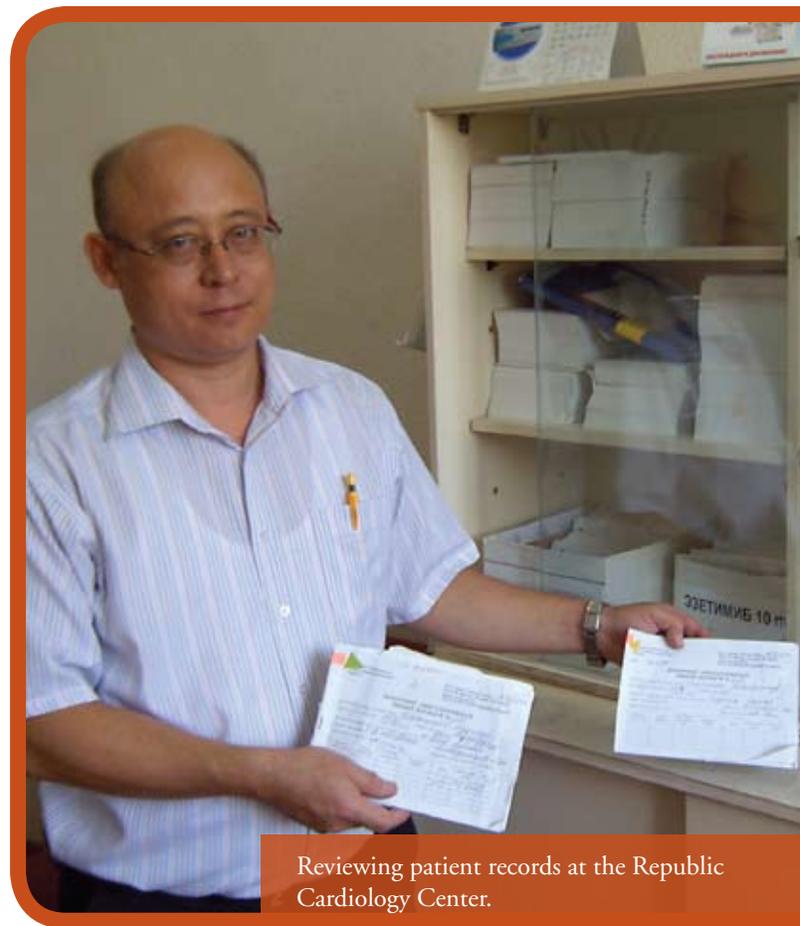
Patient monitoring for safety is important to each of the donors, Merck & Co. and Merck/Schering-Plough Pharmaceuticals, which together have provided more than \$8.7 million worth of medicines since mid-2007. AmeriCares manages the overall program and the supply of donated drugs, whose importation and distribution are handled within Uzbekistan by Soglom. The Republic Cardiology Center oversees the operational details of the initiative and reports patient stories and overall progress back to AmeriCares. The program also enjoys strong support from the Ministry of Health, which covers the cost of critically important laboratory tests for patient safety and monitoring. “The Ministry of Health’s contribution of resources, in terms of funding testing, creates more equality in the partnership,” says Gudwin. “But, more importantly, it creates a stronger trajectory with regard to the long-term sustainability of the best practices we’re trying to encourage through this program.” Beyond that, says Terry Conroy, the pharmacist in AmeriCares’ medical unit, the ministry’s endorsement of the program has added to its credibility. “They have validated the program,” she says, “especially for the patients.”

Outcomes and Adjustments

Though small as such programs go, CACDI seems to be having an impact. Between June 2007 and December 2008 it reached 642 patients, making them aware of their blood lipid levels, the need to keep cholesterol under control and the lifestyle changes essential to that end. Further, the 177 patients who had participated in the program for at least 12 months as of August 2008 saw their total serum cholesterol levels decline by an average of about 20 percent. The cardiologists treating them, meanwhile, have been trained to be focal points for the dispersal of best practices in statin pharmacotherapy for the management of hyperlipidemia. Since one of CACDI’s aims is to create centers of excellence in treating cardiovascular diseases across the country — thereby amplifying the program’s effect — it has stressed physician education. Before its official launch, the Republic Cardiology Center, a teaching hospital, hosted a training session for specialists from several regional cardiology centers that were interested in participating. The training was primarily intended to update the cardiologists on current best practices for the treatment of heart disease. At least 45 physicians have so far benefited from

the training and the opportunity to improve their qualifications, maintain high standards in patient care and follow-up, and to mitigate cardiovascular complications, such as heart attack and stroke, in their patients.

After the program started, some practices of care had to be modified, within medically acceptable limits, for the sake of affordability. Laboratory tests, especially, posed a problem. Two types of tests are essential: those used to help monitor the effectiveness of treatment and those used to identify potential serious adverse events. One of the tests — the creatine kinase (CK) assay, originally recommended as a way to monitor patients for the muscle damage occasionally associated with statin use — proved too expensive. Indeed, one hospital dropped out of the program because it could not afford the test. So the program designers chose not to require repeated CK screening. Instead, Conroy says, physicians seek to detect such problems early via clinical assessment of muscle pain. (Only those who report muscle pain during examinations need to be further tested.) If they wish to do the CK test, of course, they can, and several do establish a baseline CK reading for patients against which to compare future assays. They are just not required to report these measurements to participate in the initiative.



Reviewing patient records at the Republic Cardiology Center.

Photo by Jim O'Brien



Checking the stock of Merck-donated medicines at the Jizzak Cardiac Center.

Photo by Jim O'Brien

All physicians in the program do, however, take baseline readings of total cholesterol level and liver function, which is a means of tracking effectiveness and drug toxicity. Patients are given these tests at intervals, beginning at six to 12 weeks, and then at six months and 12 months after starting drug therapy. They are thereafter tested twice a year. The tests are not just important for monitoring the effectiveness of the treatments, says Conroy. They also demonstrate that the physicians are keeping an eye on their patients' safety and making fact-based decisions about their therapy. Most importantly, the cholesterol test results can have a powerfully positive influence on patients. The measurements are often the only tangible signal of progress they get for their efforts. "Patients don't feel their cholesterol level," says Conroy, "so the disease can progress silently. This test gives it a microphone." Watching their blood cholesterol levels slide down the chart is, Conroy notes, a powerful motivator. It helps to keep patients on the diet and exercise regimen prescribed by their physicians.

The small scope and simplicity of the program, both in terms of the testing and the enrollment, are also a plus, Gudwin and Conroy say. These aspects, they say, enhance the continuity of treatment and monitoring of patients. They do not necessarily limit the impact of the program either, they explain. Their hope is that participating institutions, dispersed as they are across the country, will act like foci from which the knowledge transferred by the program will radiate throughout the medical community.

Sustaining the Effort

From the donor's perspective, says Christine Funk, associate manager of Merck's Global Health Partnerships, it is reassuring to work with an organization that has tight oversight and management procedures. AmeriCares, she says, has strong mechanisms in place to ensure that the drugs they send to recipient countries go where they're meant to and are not diverted into the gray market. Similarly, its management at the pharmacy level is exemplary, says Funk. This eases donor concerns about expired products remaining on shelves. "We

require partners to tell us if anything goes wrong,” says Funk, “and AmeriCares hasn’t had to yet.”

Though Funk gives CACDI high marks, she does wonder how long a program of this sort should continue. Prices for generic statins have dropped by as much as 50 percent from the time they were initially introduced to global markets. “Generic simvastatin is available in Uzbekistan,” notes Funk. “It’s on the WHO Essential Medicines List, and the price is trending downward, though it is still expensive for poor people. But we, as donors, don’t want a forever and ever, open-ended commitment because, then, how do you get stability and sustainability within the country itself? Eventually, you want the health system to supply these needs for its patients. So [the question is] with the trend going in a positive

direction — how much longer do we maintain the donation program?”

The ministry’s support for the program is, in this context, particularly encouraging. It did, after all, underwrite the laboratory tests required by the program protocols. It recognizes that cardiovascular disease is a serious problem in Uzbekistan. And if AmeriCares has accomplished even half of what it hoped to do, a cadre of cardiologists is now well-prepared and primed to spread the word about best practices in the management of hyperlipidemia in Uzbekistan.

By Unmesh Kher



A patient prepares to have his blood drawn for routine lab tests.

Photo by Jim O'Brien

MAP's Globetrotting Travel Pack Program Meets a Universal Need



Lessons Learned:

- *Branding opportunities are an effective way to attract pharmaceutical manufacturers and other suppliers.*
- *Pharmaceutical partners use just-in-time manufacturing to supply medicines with usable expiration dates.*
- *An established measurement and screening program is critical to quantifying a program's health benefits and determining future needs and areas for improvement.*



Volunteers with Amazon Promise use medicines provided by MAP International at a clinic in Peru's Amazon Jungle.

Photo provided by MAP International

When San Diego-based emergency room physician Paul Dohrenwend, M.D., went to Haiti earlier this year, he went on a special mission of a dual nature. Dohrenwend went to provide voluntary medical relief to a Haitian orphanage. He also visited a Haitian child he is considering adopting.

Dohrenwend carried a special tool to assist him on his mission: the Travel Pack, a prepacked assortment of medicines and medical supplies assembled and provided by Medical Assistance Programs (MAP) International.

“Boy, did that thing take a journey,” says Dohrenwend, an emergency room doctor at Kaiser Permanente San Diego Medical Center. “First, we hand-carried it to Haiti. Then we tried putting it on top of a jeep, which we had to drive over a potholed road. But we realized it was going to fall off, so we put it and about nine people in an Isuzu trooper.”

Medicines to Many Distant Cities

Haiti is not the only place served by MAP International's Travel Pack, which has become a staple of medical relief missions. Dohrenwend himself has brought them to Baja Mexico as well as Haiti.

www.casestudiesforglobalhealth.org

The Travel Pack is a prepacked assortment of medicines designed to help treat illnesses and injuries common in developing countries. Each Travel Pack includes two boxes comprised of up to 700 treatments of antibiotics, anthelmintics, analgesics, topical steroids, rehydration salts, vitamins and other general medical supplies worth an average wholesale value of \$14,000. Physicians contribute a \$450 tax-deductible handling fee that helps MAP International recover some of the costs associated with the program. Since MAP began the Travel Pack program in 1993, the organization has shipped approximately 750 tons of medicine in Travel Packs to 115 countries, providing up to 17 million treatments. MAP estimates that it will provide 2,400 Travel Packs for medical teams traveling overseas in 2009.

The Travel Pack was born as a result of growing requests from short-term medical mission teams for medicines and supplies. The Travel Pack met the need for those teams and allowed MAP to minimize costs by using volunteers to prepack the products. The first 12 months of the program saw 442 packs shipped, and steady growth continued over the next several years, peaking at more than 3,000 shipped during fiscal year 2008. To support the heavy growth in 2008, volunteers contributed more than 2,300 hours of service in the prepack program.



Volunteers with Amazon Promise use boats to bring much-needed MAP International medicines to villages in the Amazon jungle.

Photo provided by MAP International

MAP volunteers typically put together 200 Travel Packs at a time, running the packs through an assembly line as they fill them with medicines and supplies. “It’s really an amazing process,” says Jodi Allison, senior representative for philanthropic services at MAP. “Volunteers pack medicines in a very tight, predetermined fashion so that no space within the boxes is wasted. This reduces the size of the boxes needed and, thus, reduces environmental impact, which is another one of MAP’s goals.”

Each box measures 17 by 14 by 11 inches and weighs between 20 and 30 pounds. The exact assortment of medicines varies depending on supply. After the assembly process is completed, MAP ships the Travel Pack directly to the medical professional who will be traveling overseas.

In creating the Travel Pack program, MAP has partnered with about a dozen pharmaceutical companies. Of these, GlaxoSmithKline, Merck, Schering-Plough and Wyeth all have dedicated donation programs to consistently supply MAP’s needs. Larry Morris, manager of MAP’s Short-Term Medical Mission

Program, says such pharmaceutical companies help make the Travel Pack program possible and keep each pack’s contents consistent. The incentive for each company is slightly different, but all of them benefit from getting their products into the hands of the people who need them most, often in the most remote places in the world. The many physicians who are served by the Travel Pack program gain a greater awareness not only of the products produced by the company but also of the philanthropic spirit of the company that participates. The company gains an efficient outlet to refer physicians when they ask for products to be used on short-term medical mission trips.

“MAP realizes that branding is important to our pharmaceutical partners,” he said. “We also know that the packs would not be possible without their generous donations. In order to help participating physicians recognize the key role our partners play in the provision of the packs, MAP adds our major partners’ logos to each pack.”

Morris also noted that MAP’s Short-Term Medical Mission Program, which includes both Travel Packs and custom orders, complements MAP’s Long-Term Health Development Program, which provides bulk shipments of medicines and medical supplies to partner organizations operating health care facilities overseas.

Anatomy of a Travel Pack

While Travel Packs may not be as uniquely tailored as MAP’s custom order program (see sidebar), they contain sufficient supplies to help with some of the common and important needs in the developing world.

“The Travel Packs contain medicines for treating infections, allergies, asthma and other illnesses,” Dohrenwend says. “The boxes come packed with just about everything you could want for just about everything you would treat. A lot of the diseases these children face can be treated with antibiotics, so the antibiotics that come in these packs are a major help to us. Also, many of these people, children included, are only eating rice and beans, so the vitamins are very helpful. And the oral rehydration salts are instrumental because many patients are suffering from dehydration.”

Dohrenwend also said that many of the medical needs of his Haitian patients are similar to those of his patients in Mexico, where he and other volunteers treat as many as 300 people a day. Dohrenwend makes the 30-minute drive to the clinic across the border about once every six weeks. The clinic, which lacks labs and equipment such X-ray machines, is located in a barrio comprised primarily of cardboard homes that stretch for about 15 miles along the Tijuana River.

“We see a lot of asthma and pneumonia, in part because they burn their garbage right next to the river,” Dohrenwend says. “Our patients also typically suffer from malnutrition and frequent fevers.”

The commitments of the four major pharmaceutical contributors have helped MAP maintain the program with a reliable supply of essential medicines. For instance, Merck & Co., Inc., has committed to supplying the program with three medicines in 2009 (Noroxin®, Pepcid®, and Singulair®). In order to get companies to participate, MAP identifies the appropriate products from the items manufactured by the company. MAP then develops a proposal highlighting the products they need, how many of each item will be included in each pack and how many packs they plan to ship each year. When the company agrees to support the program, MAP works with them on a shipping schedule that will allow appropriate expiration dating for each pack shipped. It will often require the companies to ship product two to three times per year.

Christine Funk, Merck’s associate manager for global public policy and corporate responsibility says, said there have only been one or two instances when Merck could not provide the entire assortment of medicines MAP requested for the Travel Packs.

Hurdles and Challenges

In addition to determining how to maintain a consistent supply of diverse treatments, MAP must also ensure the medicines have appropriate expiration dates.

“For both short- and long-term programs, it is important that MAP acquire and distribute medicines with acceptable expiration dates,” says MAP’s Morris. “For our bulk medicines, which we ship in 20-foot containers, we generally require a shelf life of at least 12 months. For short-term medical teams, a shorter shelf life of six months is acceptable because the medicines are generally used much sooner.”

While just-in-time manufacturing has eased the situation, MAP employees say that expiration dates are still an issue. Scott Ruschak, senior manager of MAP’s medicines program, says that 15 years ago the average expiration date for donated medicines was two years; that number is now less than one year. “That really limits what we can do when we ship something on the ocean, because the shipping process itself may take two months,” he says. “It means we have to look harder for medicines with a longer shelf life.”

According to Dohrenwend, the demand for medicines on these short-term missions sometimes outstrips the supply available within one Travel Pack.

“We voluntarily supplement these packs,” Dohrenwend says. “For instance, we may go to Costco to buy the industrial-size Ibuprofen. And the Travel Packs contain Tylenol, but sometimes we need more because it is the medication we distribute most for fevers and pain. In addition, vitamins are very beneficial to people who are usually on a diet of rice and beans. So, more vitamins would be helpful.”

Dohrenwend also suggests that MAP or other nongovernmental organizations investigate how to use short-term medical teams to help with vaccine-preventable diseases. It would be very simple to save a number of young lives, he says.

Quantifying the Unfathomable

MAP measures the value of its Travel Pack based on the wholesale value (determined by Red Book) of the products included in each pack. The value of a Travel Pack differs since it is determined by a rotating supply of medicines and medical supplies based on what MAP receives for donation. The average value is \$14,000.

MAP worked with a licensed pharmacist who calculated that volunteer physicians have provided up to 700 medical treatments using the contents of a single MAP Travel Pack. This number was determined by examining the contents of an average pack and the treatments included in each.



Photo provided by MAP International

Another difficulty MAP has encountered involves measuring the larger impact of the Travel Pack program on communities that medical teams serve. While the organization has a successful screening program and may know which three bottles of Singulair or Noroxin went to Peru and with whom, due to the remote areas in which treatment takes place, MAP is not always able to capture outcomes.

“Medical teams are more concerned with providing compassionate care to those who have lined up outside their makeshift clinics,” says MAP’s Ruschak. “Having the teams, which visit these communities on a short-term basis, quantify their impact is a challenge. For many communities, there are few, if no other alternatives.”

Ruschak and other MAP staff members perform regular field assessments to speak with key hospital staff and other officials to learn about a region’s medical needs. However, Ruschak says it is impossible to visit all of the more than 115 countries MAP serves.

Morris says MAP’s long-term program was better equipped to assess impact and numbers of patients treated. “Our clinic and hospital supply program is better positioned to document how many patients receive the benefit of MAP-supplied medicines,” he says. “With the short-term mission program like the Travel Pack, we prefer to speak in terms of the number of treatments we are able to provide.”

Dohrenwend says that counting treatments is an easy way to quantify the benefits of the program. “If each pack contains 700 medical treatments, each dose saves or improves a person’s life, so each pack contributes to 700 lives, I would say. Take even something as simple as an oral rehydration solution. If a kid has diarrhea, you save his life with it,” Dohrenwend says.

Others, such as MAP’s Ruschak, draw conclusions from data gathered by other organizations, such as UNICEF. UNICEF reports that in Haiti, which is one of the top two destinations for Travel Pack users, pneumonia causes 20 percent of deaths among children under age five.

Still, MAP and its physician clients experience difficulties in applying supply-chain science as best as possible in a human world, Dohrenwend admits. “For example, one of the biggest killers in Africa is cholera. How people respond to cholera is pretty random; perfectly healthy people die quickly, while sick people might make it through. There’s no way of quantifying who will make it through in a situation like that,” he says.

Morris says the issue is difficult. “How can we know when something could be done better or what can be improved?” he asks, noting that MAP’s thorough qualification process is one source of data. “This is a phenomenon that is taking place in short-term missions as a whole in this country. There are about two million individuals participating in short-term missions, including medical missions, in the United States each year.”

However, Morris also says that MAP is in the process of increasing its data-gathering faculties. “We just completed a survey process that will hopefully address this very issue,” he says. The survey allows physicians to assess and grade the contents of the Travel Packs, give feedback as to what is and is not essential, and recommend additional medicines to include. MAP provides the survey to medical providers after they return from Travel Pack trips.

By John Otrompke, J.D.



Photo provided by MAP International

Other MAP Programs Provide Greater Flexibility and Unique Branding Opportunities for Suppliers

While the Travel Pack may be one unique product MAP has developed since it expanded from long-term medical relief, the organization also offers health care providers a number of other products as well. Here is a summary.

Custom Order Program

The Travel Pack is actually one of two integrated components within MAP's Short-Term Medical Mission Program. The Custom Order option allows the mission teams to supplement their mission pharmacy needs with medicines and supplies on an a la carte basis, outside of what is available within the Travel Pack.

"The Travel Pack has its limitations regarding emergency disaster response," says MAP's Larry Morris. "When a disaster hits, the kind of medical needs that exist can be very different from one disaster to another depending on what kind of disaster has struck. We respond to relief situations uniquely, however, so that the Travel Pack is not a square peg we're trying to fit in a round hole.

"For example, when Cyclone Nargis hit Myanmar last year, as part of our own relief efforts, we sent several Travel Packs. We have them on the shelf so they're ready to go. But when the storms went through Haiti last year, we responded by partnering with medical teams and quickly supplied them with customized medical packs."

Future growth within the Short-Term Medical Mission Program could include other specialty prepacks, such as pre/post natal vitamin packs, as well as expanding the inventory selection with the custom order option.

The Johnson & Johnson Medical Mission Pack

Among other manufacturers, Johnson & Johnson Family of Companies has two unique products with MAP. One, called the Johnson & Johnson Medical Mission Pack, includes the company's Tylenol products and other over-the-counter medicines. In addition, the Johnson & Johnson Medical Mission Pack Plus includes over-the-counter medications as well as antibiotics and other prescription products.

ETHICON Products

Johnson & Johnson subsidiary Ethicon also supplies products to MAP, but they aren't medicines. They're sutures. In fact, Ethicon provides about 182 types of sutures from which physicians may choose. Morris said physicians use the products for operations ranging from hernia surgeries to repairing children's cleft palates. For this service, providers contribute to MAP a tax-deductible \$35 service fee.



Global Interagency Efforts Stem Counterfeit Drugs in Greater Mekong Asia



Lessons Learned:

- *Submit an early request for clearance in each country and follow up with constant communications to prevent delays in formal country clearances and in completing financial transactions.*
- *Starting on the first day of the project, invoke a sense of ownership among all parties to ensure unfettered collaboration.*
- *Reevaluate technical requirements and make sure people on the ground are well-trained and have enough equipment to do their jobs effectively.*
- *Check the collaborative chain for weak links. It isn't enough for agencies, governments and law enforcement to agree to work together. The technology and mechanisms for cooperation must also be in place.*



Sokpheap Cambodia Pharmacy

Photo by Chris Raymond

Drug-resistant strains of a variety of potentially fatal diseases are appearing globally at an alarming rate. Can the lessons learned in eradicating poor-quality medicines that helped create particularly virulent and drug-resistant malaria strains in the Greater Mekong be used to prevent the rise of new strains in other diseases?

In the Southeast Asia/Western Pacific area, an estimated 10 to 35 percent of medicines are improperly made or illegally produced and sold. The area's high burden of malaria and elevated resistance rates to treatment are, in many cases, directly attributable to the proliferation of poor-quality medicines. Substandard medicines allow the malaria parasite to survive and then develop resistance to existing treatments. Beyond the loss of life suffered immediately through the distribution of subpar medicines, a breeding ground for highly virulent and resistant strains develops, from which untreatable disease can eventually spread to kill thousands in many nations.

Finding and eradicating poor-quality drugs in the five-country region — Cambodia, Thailand, Lao People's Democratic Republic (Lao PDR), Vietnam and Yunnan Province in China — has proven an exhausting exercise. Medicines are sold across all five countries in public (hospitals, health clinics and posts), private (hospitals, clinics and pharmacies) and informal (illegal outlets) sectors making drug collection, sampling and enforcement particularly challenging.

In an effort to combat the problem throughout the region and across its many borders, the United States Pharmacopeia Drug Quality and Information Program (USP DQI) has closely collaborated with the United States Agency for International Development (USAID)/Regional Development Mission for Asia (RDM-A); the USAID/Cambodia Mission; and the Ministries of Health of Cambodia, Thailand, Lao PDR, Vietnam and Yunnan Province (China). Together these organizations battle the



Trainees practice visual examination in Vietnam.

Photo by Chris Raymond

devastating effects of counterfeit and substandard medicines readily available in the Mekong region.

At the requests of USAID/RDM-A, USAID/Cambodia Mission and the ministries of health throughout the region, USP DQI developed a framework to support the governments in their quest to improve the quality assurance and quality control (QA/QC) of their medicines and create a comprehensive, sustainable program to build technical capacity. The process required cooperation and integral collaboration between each country's ministry of health (MOH), medicines regulatory authority (MRA), national medicines quality control laboratory (NMQCL) national priority disease control programs, surveillance site staff and, in some instances, community health care workers. USP DQI secured commitment from each through the drafting and signing of memorandums of understanding from the beginning in 2003 until 2007. Currently, the organizations use contract agreements that outline what USP DQI will provide and what the MRA and MOH of the respective country will carry out each fiscal year.

Through close partnerships with country MRAs, NMQCLs and national disease control programs for malaria, tuberculosis and HIV/AIDS, USP DQI develops yearly work plans of proposed activities. The USAID missions make decisions on which agreed-

upon activities to fund and in what amount; USP DQI oversees implementation of all activities according to an accepted time line, making regular field visits to provide guidance and monitor progress.

Counterfeit drugs are defined as those that are deliberately mislabeled to obscure source and product identity. Some of these are perfect mirrors of the drugs they copy; many more are not. Substandard drugs are defined as legally branded or labeled but the quality falls below international standards on quality, purity, strength or packaging. Most commonly, substandard medicines have one or more of the following qualities:

- lack an active ingredient but inactive ingredients are harmless,
- found to have poisonous or harmful ingredients,
- manufactured in poor conditions or smuggled past authorities,
- obtained registration in country because the medicines regulatory agency was weak and could not properly evaluate the application.
- have been improperly stored and/or transported resulting in a tainting or reduction in strength of the active ingredient.

Since 2003 the Mekong region monitoring program has grown from 17 to 39 sites and has broadened to include antimalarial, antiretroviral and antituberculosis medicines, as well as oseltamivir

(for treatment of avian influenza) and some commonly used antibiotics. Through information gleaned from the USP DQI monitoring program, countries have fined sellers of counterfeit medicines, closed pharmacies, confiscated products and issued regulatory warnings and notices to alert health professionals and the public.

From Assistance to Arrests

In 2003 USAID asked USP DQI to provide technical assistance to the ministries of health of these five Southeast Asian countries. In response, USP DQI developed a framework to support the governments in improving the (QA/QC) of their medicines. The USP DQI also helped each government create a comprehensive, sustainable program to build technical capacity.

USP DQI began by assessing the existing systems of each country, including drug registration, quality-control laboratories, procurement, storage and distribution, and post-marketing surveillance efforts. It then collected data from the field on specific antimalarial drugs to determine the quality of medicines in the marketplace, present findings of gaps or weaknesses and design individualized plans for improvement based on each country's priorities. After assessments were completed, USP DQI launched the Antimalarial Medicines Quality Monitoring Program in the Mekong subregion. The newly designed protocol leveraged established sentinel sites.

In Cambodia, Lao PDR, Thailand and Vietnam, USP DQI works closely with each country's ministry of health; relevant government agencies, primarily the MRAs; various institutions; and national disease control programs for malaria, HIV/AIDS and tuberculosis; national medicines quality-control laboratories; World Health Organization; and INTERPOL. In Cambodia, Laos and Vietnam, USP DQI supported the creation of interministerial committees consisting of MOH, ministry of finance/customs, ministry of interior/police, ministry of trade and prosecutors to collectively work against counterfeit drugs and illegal outlets.

The USAID/RDM-A and the USAID/Cambodia Mission have funded all related medicine quality-monitoring activities in Cambodia, Vietnam, Lao PDR and Thailand since the program began in 2003. Work in Yunnan Province of China was discontinued in 2005 due to political sensitivities between the U.S. and Chinese governments upon discovery of fake artesunate samples found there.

Since monitoring began in 2003, more than 4,700 samples have been collected and tested. USP DQI has supported and encouraged collaboration among the ministries of health, other country ministries and enforcement-related agencies to act on negative results.

In one example, USP DQI contributed to Operation Jupiter, an international enforcement action, by supplying sentinel site data of medicines that were collected and tested as part of the Mekong Region Medicines Quality Monitoring program. INTERPOL and WHO coordinated the various partner efforts. Evidence from chemical, mineralogical, biological and packaging analysis suggested that at least some of the counterfeit artesunate was manufactured in southeast China. This evidence prompted the Chinese government to act quickly against the criminal traders with multiple arrests and the seizure of approximately \$2.7 million worth of antimalarial products.

In another example: INTERPOL seized more than \$6.65 million of counterfeit medicines, some of which were for treatment of malaria, HIV/AIDS, tuberculosis and other common infections in Southeast Asia in 2008 and made 27 arrests, disrupting the region's fake drug trade for the second time in three years. The five-month investigation, Operation Storm, involved almost 200 raids across Cambodia, China, Laos, Myanmar, Singapore, Thailand and Vietnam. Under Operation Storm, police seized more than 16 million pills, including fake antibiotics for pneumonia and child-related illnesses. The USP DQI program exposed the counterfeit antibiotics and, working with country governments, provided the pertinent information to INTERPOL to initiate investigations.



USP DQI focal point in Vietnam is collecting samples at retail outlets.

Photo by Chris Raymond

As a result of these and other measurable actions, the QA/QC protocol that evolved has served as a model for activities in an additional 21 resource-limited countries. This protocol was first introduced into the Mekong region in 2003 and was presented in 2004–2005 to USAID missions in other countries and regions and to other donors to attract funding and support. The process, framework and methodology used in the Mekong region has since been transferred — with some adjustments to fit any given country’s specific situation — to other countries in Africa and Latin America.

From Design to Results

Results from the program are encouraging. Data collected in 2004 revealed the wide availability of poor-quality medicines. Most notably, up to 44 percent of samples of artesunate, an antimalarial drug, contained no active ingredient. In 2008, this figure dropped below 20 percent. Of the 358 antimalarial samples collected and tested, only 40 (11.2 percent) samples failed quality testing. Results provided incentive for medicines regulatory authorities to expand the USP DQI monitoring program.

USP DQI has designed country-specific sampling protocols plus supplied necessary laboratory equipment and reference standards for testing and trained almost 2,500 individuals to date. Additionally, it has facilitated numerous local and regional meetings to benefit communications among principals. The country governments that have requested USP DQI assistance state that their motivations are to improve health conditions in their nations, reduce the prevalence of counterfeit and substandard medicines, and restore public confidence in their ability to ensure safe, effective medicines in the marketplace.

Since sophisticated laboratory facilities are rarely available in the field, USP DQI teaches simple, practical methods for early detection of substandard and counterfeit drugs. To reach rural areas where the disease burden is generally higher, USP DQI supplies surveillance sites with portable laboratories, known as Minilabs, designed by the Global Pharma Health Fund. The Minilabs contain the necessary equipment, reagents and secondary reference standards to test medicines for presence and content of the active ingredient and its ability to disintegrate properly.

Local analysts, usually pharmacists and community health workers from ministries of health, are trained to perform basic tests: visual inspection, disintegration and thin layer chromatography, for example. In addition to basic tests, USP DQI has also designed a protocol and training program in sampling techniques.

The 37 active sentinel sites in the Mekong region were selected in close collaboration with each country MOH based upon its specific national priorities. Some sites were chosen due to substantiated or anecdotal evidence on the prevalence of counterfeit medicines, especially at the border areas, which are prone to illegal activity. Other sites were targeted due to the high burden of malaria or elevated resistance rates to malaria treatment, which can indicate the presence of poor-quality medicines.

But this is not to say that the project has proceeded unimpeded by obstacles. Implementing medicines quality monitoring at the country level has been slow at times, primarily in the initial stages, according to USP DQI officials. Collaborating with four separate country governments greatly magnified normally “simple” challenges, such as processing equipment and supplies through time-consuming formal country clearances, completing financial transactions, and making arrangements to the satisfaction of all parties. Differences in country quality assurance/control systems and language barriers — which could become confusing in the translation of sampling and testing protocols, for one thing — added another layer of delays.

Despite careful planning, a few unwanted surprises appeared along the way. For example, technical issues surrounding sampling procedures and testing developed in areas USP DQI had not anticipated. Some rural area sites had difficulty collecting the required quantity of samples for testing and verification, and some countries lacked adequate equipment at the national laboratory to carry out verification testing. From field visits, it also became apparent that some of the trainees needed further reinforcement of basic sample collection and testing skills. To overcome these challenges, USP DQI amended the sampling protocol; reduced the number of units per sample to be collected; provided necessary lab equipment, reference materials, reference substances and reagents;



Christopher Raymond demonstrates Minilab to INTERPOL inspectors.

Photo by Chris Raymond



Family in clinic in Stung Treng Province, Cambodia.

Photo by Chris Raymond

trained sample collectors on analytical methods; and conducted refresher training for field staff.

Forming a Multi-Dimensional Partnership

The relationships between many of the agencies have cemented over time and through many projects. The United States Pharmacopeia is a 185-year-old, not-for-profit public health organization whose mission is to improve the health of people around the world through public standards and related programs that help ensure the quality, safety and benefit of medicines and foods. The USP DQI program, a cooperative agreement between USP and the U.S. Agency for International Development, focuses on advancing the health care of people in resource-limited countries.

USP DQI has maintained a longstanding relationship with USAID regional and country missions and takes an active role in the agency's annual process of scheduling and budgeting activities through approved work plans. The work plan process is a collaborative effort in which all partners participate to determine priority activities. Separate work plans are proposed to each participating USAID mission and then reviewed collectively in

a regional partners' meeting to eliminate duplicative efforts and to coordinate activities. The process is similar with any other agency funding USP DQI projects, such as the World Health Organization.

USP DQI determines in which countries activities will take place and where technical assistance is most needed. The USAID missions make decisions on which agreed-upon activities to fund and in what amount; USP DQI oversees implementation of all activities according to an accepted time line, making regular field visits to provide guidance and monitor progress.

USP DQI's medicines quality monitoring project in the Mekong region is funded primarily by the USAID/RDM-A and USAID/Cambodia Mission. Supplementary funding on topical aspects, for instance, testing the quality of medicines for avian influenza, may be provided by USAID/Global Health Bureau, Office of Health, Infectious Diseases and Nutrition.

Despite the effectiveness of this extraordinary web of collaborators, relationships can and do remain delicate and occasionally lack



A Cambodia Undersecretary of State speaks with an unlicensed drug seller.

Photo by Chris Raymond

conformity. Although all five countries experience many of the same problems, common goals and the willingness to work for common good are often lacking. Some key partners lack the financial resources for collaborative activities or the motivation to cooperate.

To bring the principals together and build alliance, USP DQI helped key partners find common ground and the trust to share data through numerous face-to-face meetings. USP DQI initiated discussions to obtain their support and encouraged their involvement as an integral part of the USP DQI project management team. This approach has created a sense of ownership in the program among the partners and resulted in demonstrated efforts of mutual cooperation.

Sharing information among relevant agencies within a country and between countries has been slow and ineffective, particularly among national law enforcement agencies and among medicines regional authorities, report USP staff. Consequently, when counterfeit or substandard samples are discovered in the field, weak or nonexistent information-sharing systems can further delay action. Some of the factors that contribute to the problem stem from

underdeveloped human resources, fewer technology resources and poor or restrictive regulatory procedures. In many cases, the main problem is there are no effective mechanisms for collaboration in place. USP DQI had to make the case for collaboration and then help build the bridges needed for the collaboration before the primary work could begin.

The Future

USP DQI's future plans involve making medicine quality monitoring sustainable within each country's own governmental construct. To that end, the plan calls for the MOH, MRA and NMQCL to gradually pick up the costs of sampling collection, testing and necessary reagents, reference standards, supplies and travel plus payroll costs for associated staff time. USP DQI and USAID hopes that these programs will become self-sustaining in the foreseeable future.

Meanwhile, USP DQI will be working with the ministries of health and other stakeholders to explore possibilities for leveraging other sources of funding such as from The Global Fund to Fight Aids, Tuberculosis and Malaria, and WHO. DQI could help the country develop a proposal to The Global Fund, for example, together with

WHO and the ministries of health, to include key aspects of QA/QC of medicines. These efforts work toward eventual government sustainability and, thus, gradually phase out activities that donors will fund.

Beyond these measures, USP DQI's future plans call for project expansion in both scope and reach:

Supporting regional or south-south collaboration and capacity building: Regional support can play an important role in strengthening national capacity and ensuring its sustainability. In this context, the USP DQI program plans to build sustainable capacity, where appropriate, by establishing regional centers of excellence that can serve as a technical resource in quality assurance of medicines for less-developed countries in Latin America, Africa, Southeast Asia or any other applicable region.

Participating in international initiatives to combat substandard and counterfeit medicines: USP DQI provides technical assistance in the form of training, facilitation of communication and reporting field sampling and testing data to INTERPOL. A primary objective of this collaboration is to assist in providing evidence for enforcement actions taken by INTERPOL, customs and police resulting from data generated from medicine quality

monitoring programs. These actions are designed to disrupt the international trafficking of illegal, counterfeit and unregistered drug products in countries where USP DQI has a presence.

Increasing community outreach to raise awareness about counterfeit and substandard medicines: In collaboration with nongovernmental organizations (NGOs) that provide community-based services and other local players, such as pharmacists, USP DQI will attempt to raise public awareness through community outreach. Often, the first person patients seek for medicines and medical advice is a community pharmacist; in some countries, there is a lack of enforcement or an inability to disseminate information on poor-quality medicines. In such cases, it is necessary to reach the public through alternative routes.

USP DQI's plans include working with a broad spectrum of global partners and expanding collaborations with international organizations and country partners. Some of the organizations include: WHO, USAID, the Bill & Melinda Gates Foundation, The Global Fund, INTERPOL, MeTA Alliance, and many local nongovernmental organizations, among others.

By Pam Baker



Members of the President's Malaria Initiative team were accompanied by Dr. Souly Phanouvong of USP DQI on visits to two cross-border provinces — Chanthaburi, Thailand, and Pailin, Cambodia (shown) — both high malaria-resistance emergence areas where USP DQI has medicines quality monitoring activities.

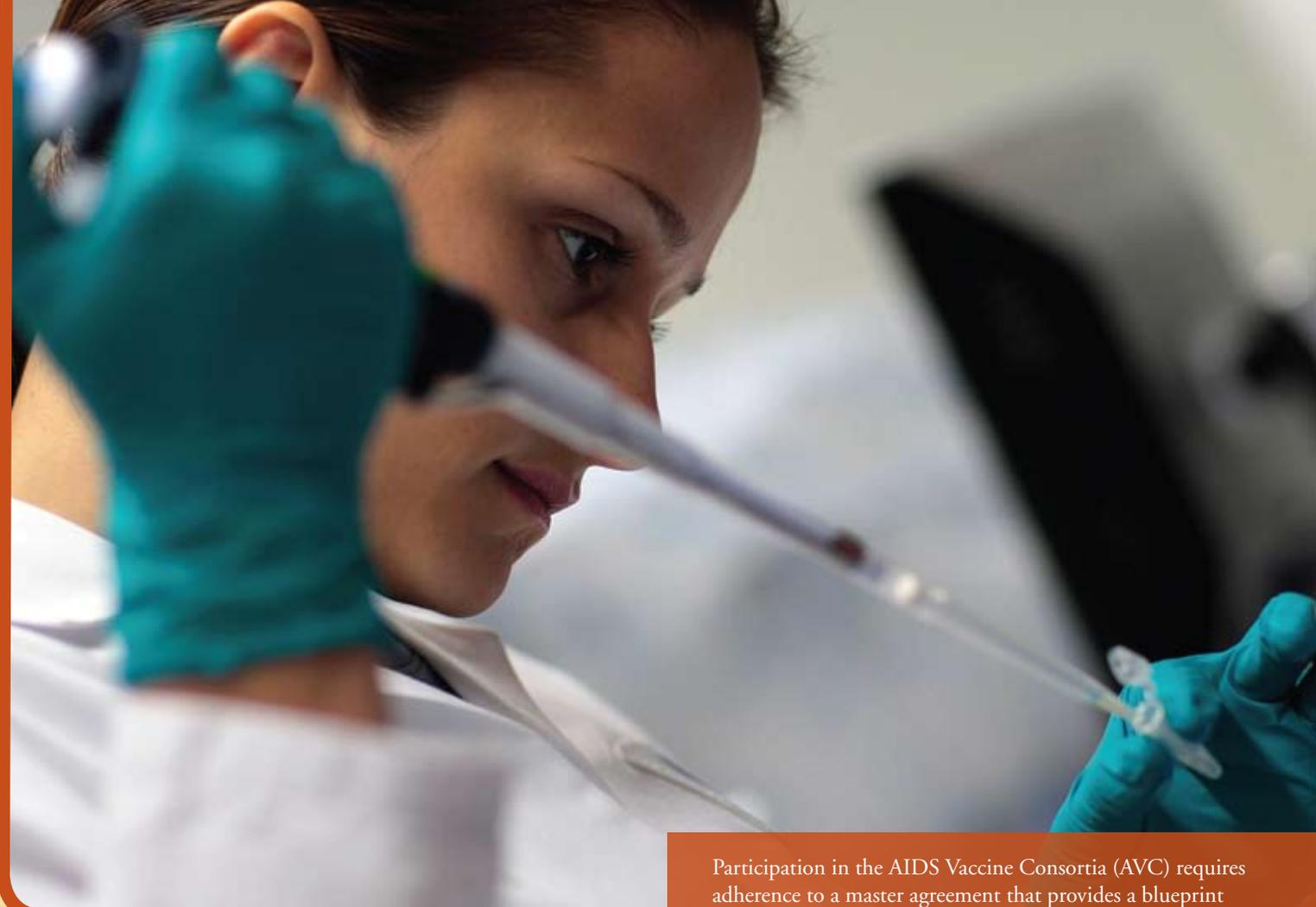
Photo by Souly Phanouvong

Breaking Down the Barriers to Sharing Knowledge



Lessons Learned:

- *Innovative collaborations that include flexible research teams from different institutions help to provide new insights into the vaccine puzzle.*
- *Collaborations require open communications between members and strong scientific leadership.*
- *Special agreements that allow sharing of intellectual property rights are an essential foundation.*
- *Strong administrative and financial support enable the collaboration's researchers to focus on going beyond the mainstream.*



Participation in the AIDS Vaccine Consortia (AVC) requires adherence to a master agreement that provides a blueprint for the AVC research program and the set intellectual property procedures.

Photo by Chris Hondros/Getty Images

Developing an HIV vaccine has proved a very difficult project. The International AIDS Vaccine Initiative (IAVI) has, in response, created a model scientific collaboration to search for breakthroughs. The IAVI AIDS Vaccine Consortia started with a consortium to create a vaccine that would elicit neutralizing antibodies. It has since added two more. The consortia act as virtual laboratories consisting of geographically distant researchers who readily share their findings across institutional boundaries. A major startup issue was developing an intellectual property master agreement that dovetails with the policies of the researchers' institutions. The agreement grants IAVI an option to license program inventions while giving all participating organizations a share of any future licensing revenues. IAVI provides secure financing and covers most of the administrative work, thus freeing scientists to focus on their research to an unusual degree.

HIV presents a formidable challenge for vaccine developers. To block the virus' invasion, immune responses have to target constantly shifting viral proteins. In terms of viral diversity, "If flu is my fist, then HIV is the size of this room," says Seth Berkley, president of IAVI. In addition, the HIV envelope is wrapped in a mantle of captured human cell membrane material. This mantle protects viral particles from immune recognition and attack. Finally, there is no adequate animal model for HIV infection.

IAVI was founded in 1996 to promote development of a globally affordable and accessible HIV vaccine. It supports HIV vaccine research by partnering with academic, corporate and government institutions. Since 2001, it has also developed its own research facilities.

HIV has proved too complex for the individual investigators trying to develop novel solutions in his or her separate institutions. IAVI emphasizes the use of "industrial-style project management" to

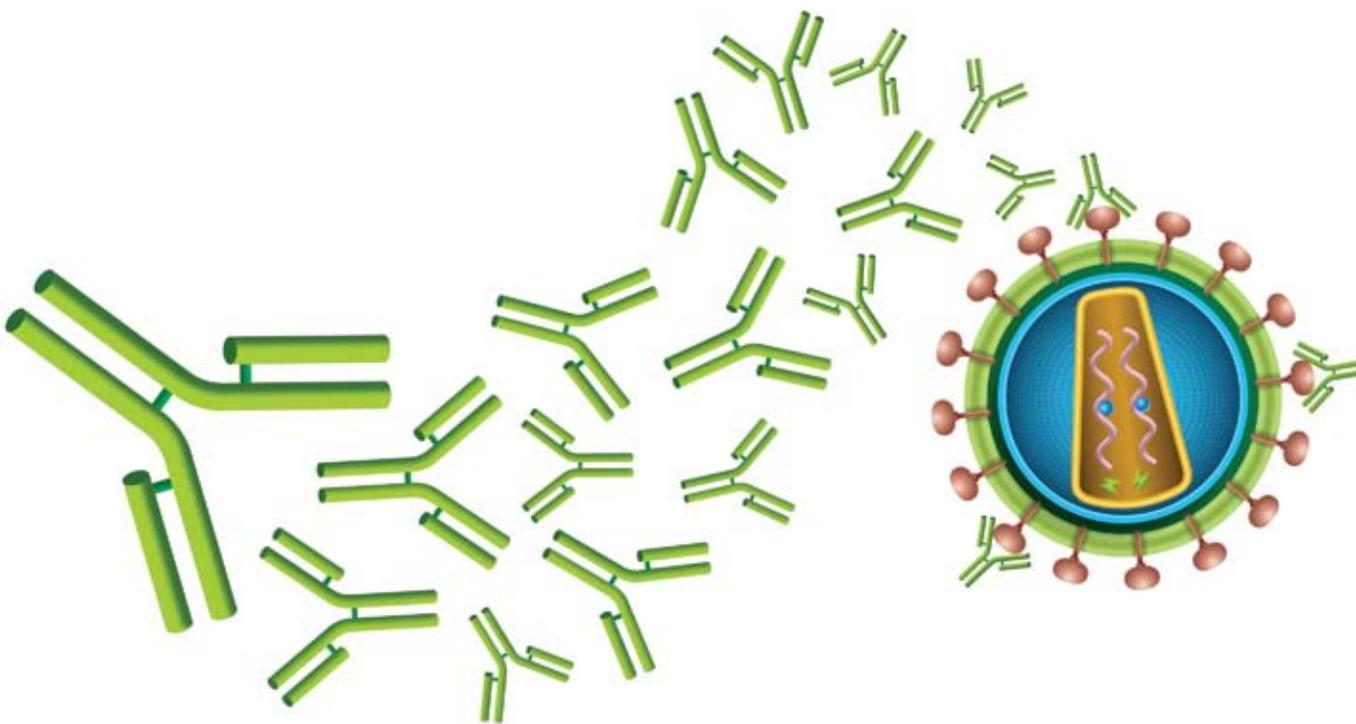


Illustration of neutralizing antibodies attaching to HIV

Credit: Samuel Velasco/5W Infographics

prioritize the most promising vaccine strategies and quickly form ad hoc teams to investigate them.

To facilitate this interorganizational collaborative approach, IAVI has created a system known as the AIDS Vaccine Consortia (AVC). By 2009, the AVC network combined the efforts of researchers at 21 organizations across the globe.

Creation of the Neutralizing Antibody Consortium

Traditional vaccines teach the body to produce antibodies against the virus in question. Antibodies are Y-shaped proteins tailored to attach themselves to specific viral proteins. Neutralizing antibodies can block the virus from entering cells and reproducing. HIV researchers in recent years have largely focused instead on “cell-mediated immunity.” This part of the body’s immune defense involves white blood cells that eliminate cells already infected by viruses. But vaccines based on cell-mediated immunity, such as the one Merck had to abandon, have had disappointing results so far. The generated immune responses have been too weak, nor could they compensate for the shape-shifting propensity of HIV proteins even if they had been stronger.

At the beginning of this decade, Wayne Koff, IAVI’s senior vice president for research and development, decided to take another look at antibody research. Papers published in 1999 and 2000 showed that administering antibodies completely protected uninfected macaques. Koff says that when IAVI surveyed the ongoing research, “We found many investigator-initiated small grants and no industrial-style, mission-oriented programs.” In line with Koff’s critique, IAVI established the Neutralizing Antibody Consortium (NAC) in 2002. The initial consortium included researchers from four institutions: The Scripps Research Institute (La Jolla, Calif.), the University of Pennsylvania School of Medicine (Philadelphia), Weill Medical College of Cornell University (New York City) and the Dana-Farber Cancer Institute (Boston). In addition, the NIH’s National Institute of Allergy and Infectious Diseases (NIAID) agreed to support the consortium through its Vaccine Research Center.

IAVI fully funded the consortium startup with its own resources. It has continued to do so over the years, allowing NAC members to spend more time in the lab and less in the office writing grant proposals. Robert Doms, the initial NAC researcher at the University of Pennsylvania, says that he was delighted with the financial freedom the consortium provided. “IAVI has allowed me

to concentrate on more risky research,” he says. In contrast, “The NIH tends to put its outside grants into further developed, less speculative projects.”

The NAC became a virtual research center. It provides a means for the scientists to share their thoughts and observations across institutions. “In forming the NAC, groups agreed to several basic principles,” says Koff. “These included early sharing of data, candor around the table and shared intellectual property. We wanted to ensure that all members would benefit from the consortium’s success and that the developing world would have access to a vaccine.”

The NAC has since grown to 15 member institutions, including organizations in the U.S., Europe and Asia. It has established four priorities based on the research gaps members noticed. These are: understanding antibodies’ molecular activity, elucidating the interaction between HIV proteins and antibodies at the atomic level, developing technology to assist in vaccine design, and screening HIV protein sequences for use in a vaccine. The order of these priorities shifts from year to year as research proceeds.

Two New Consortia

Building on the NAC model, IAVI has added two new consortia in recent years. Members of each consortium include different subsets of the NAC membership plus several new organizations.

In 2006, IAVI established the Vector Consortium (VEC), which now has eight institutional members including IAVI. Like the NAC, the VEC covers a neglected aspect of HIV vaccine research. In the interests of safety, HIV vaccines under development generally utilize genetically engineered viruses (viral vectors) that do not cause major disease in humans. These viruses are altered to carry HIV proteins and to be nonreplicating. Their ability to provoke a protective immune response has turned out to be rather weak. The VEC’s purpose is to investigate replicating viral vectors. “We are looking at most stimulating kinds of vectors, the live vector ones and work on how we would create a useful vaccine,” says Koff.

If replicating viral vectors pose some danger of causing disease, an attenuated HIV vaccine causes even more shivers. Such a vaccine might turn out to be not so attenuated in some people, resulting in HIV disease. This problem occurs with the live polio vaccine. Yet the only vaccine that has proved protective in a monkey model is an attenuated virus. (That vaccine was fully protective only against the same strain of virus as was in the vaccine. It also caused immune deficiency in some monkeys.) IAVI initiated its Live Attenuated Consortium in 2007 to study the immune response to this type of vaccine. The consortium hopes to learn what the key

elements are that make the attenuated virus vaccines protective. Researchers could then apply the lessons learned when designing safer candidate vaccines.

A New Regime for Intellectual Property

Intellectual property (IP) rights are critical to IAVI’s goal of ensuring that an HIV vaccine reaches developing countries at a reasonable price. Achieving this goal required considerable ingenuity when drawing up the consortia’s master agreement. IAVI and the other founding institutions constructed a durable IP arrangement that grants IAVI the option to license any AVC inventions including enabling background technology. Revenues resulting from development of these inventions will be shared within each consortium according to an agreed-upon formula. “It took two years of negotiations to hammer out the IP details before executing the master agreement,” Lita Nelsen, director of the Technology Transfer Office at the Massachusetts Institute of Technology, advised the nascent NAC. The agreement went through 10 or 12 preliminary drafts. Nelsen says, “Traditionally, universities collaborate but recognize that they have competing interests: what’s mine is mine and what’s yours is yours. But here, the researchers just wanted to end a world scourge. Good will can accomplish a lot.” The consortium concept offered a number of financial and organizational benefits, so the researchers pushed to make it work.

IAVI receives an exclusive licensing option for any discoveries in return for funding the research. If IAVI decides to exercise its option, it pays the patent application fee and gets the rights in the area of HIV vaccines. The inventing institution receives the largest share of any royalties that result, and IAVI receives a smaller share. The remaining royalties are split among the other consortium members. “The agreement keeps people at the table, sharing their ideas. If anyone makes an invention, well, they likely would not have gotten there without the team brainstorming,” says Koff. The issue becomes more complicated if multiple institutions contributed concretely to a particular invention. If that is the case, all the contributing organizations share in the major inventor’s portion of the revenues. IAVI’s patent counsel is available to help resolve patent issues.

All new consortia members have to make a commitment to the AVC research program and the set IP procedure. As agreed by the founding members, participation requires accepting the master agreement on a take-it-or-leave-it basis. A separate Cooperative Research and Development Agreement (CRADA) governs the research contributions of the NIH, NIAID’s Vaccine Research Center. The CRADA states the U.S. government’s standard technology transfer and licensing terms. In 2007, IAVI signed another supplementary agreement with the Indian government’s

Department of Biotechnology (DBT). This agreement allows the Neutralizing Antibody Consortium to work with two Department of Biotechnology-funded institutes. It also envisions using Indian manufacturers to produce reagents for vaccine design.

One alteration to the consortia's master agreement took place in 2007, when the VEC received a major grant directly from an outside source, the Bill & Melinda Gates Foundation's Collaboration for AIDS Vaccine Discovery (CAVD). The Gates Foundation requires prompt dissemination of CAVD-funded findings and materials to the broader scientific community so as to speed HIV vaccine research. It also requires that any vaccine arising from CAVD research be accessible to people in developing countries. Since the Gates Foundation requirements are consistent with IAVI's standard policies, they did not greatly alter the sense of the AVC's master agreement.

Organizational Structure

IAVI ultimately incorporated the three consortia into a single organizational structure, the AVC. A management committee composed of senior IAVI scientific executives oversees AVC operations. This committee reviews the work of the participating research centers and sets organizational priorities to improve integration and efficiency. It also helps revise the research agenda for each consortium, whose work plan is supervised by each consortium's individual scientific director (or a consortium executive committee in the case of the NAC).

These scientific directors are critical to the operation of each consortium. They supervise the science program and consult with consortium members on a daily basis. They also conduct frequent work meetings as well as a larger AVC science update meeting. Researcher recruitment is another task within the scientific directors' responsibility. The directors put together a coherent group to achieve the consortium's goals, adding new members to fill any gaps that appear. They are, therefore, in charge of building the critical team spirit for the collaborative effort.

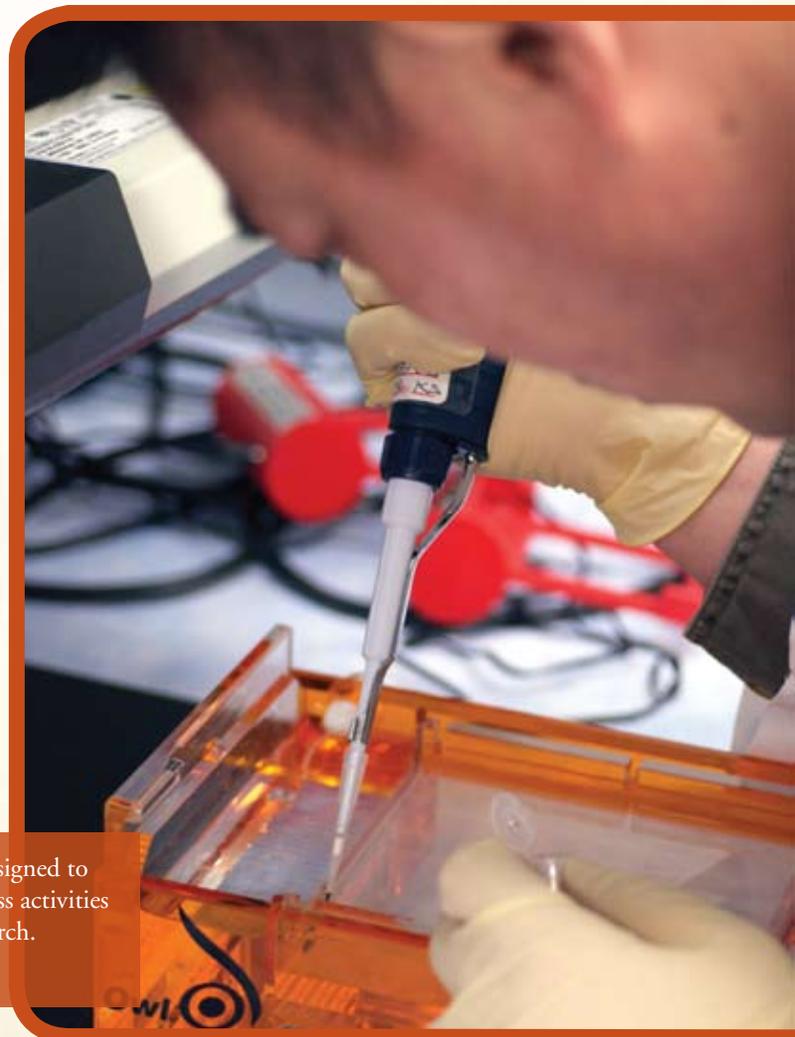
Koff, who is also the AVC executive director, says that, overall, "The idea is to relieve the researchers of the grunt work and free them to do the science." IAVI's Business Development Department has developed agreements with contractors to do the standard

evaluations to expedite data management. The business team also draws up material transfer and licensing agreements needed for research materials such as antibodies, reagents and delivery systems for animal testing. Finally, it manages the licensing of IP coming from the AVC.

Each consortium has an IAVI-hired project manager, too. These project managers work with the researchers to obtain needed testing and materials outside the consortium. They also complete a lot of the standard paperwork and reports.

Extending the Collaboration

IAVI's Clinical Protocol G Program is a major ongoing NAC-related project that illustrates how the collaborations within the AVC are branching out. This study is screening antibody samples from 1,200 people with HIV spread across Africa, Thailand and the United States. So far, two new potent broadly neutralizing antibodies have been discovered.



The AIDS Vaccine Consortia model is designed to relieve researchers of nonscientific, business activities in order to free them to do scientific research.

Photo by Julianna Thomas Photography

Beyond the NAC, Protocol G involves participation by an international network of Clinical Research Centers organized by IAVI as well as outside research institutions. Neutralizing antibodies uncovered by IAVI and its collaborators will aid vaccine design work at the NAC and elsewhere. In the meantime, the work on Protocol G has further honed the capabilities of the Clinical Research Center's network during a dry spell in actual vaccine trials.

In a move to expand the NAC's work, in September 2008 IAVI and The Scripps Research Institute announced the establishment of the IAVI Neutralizing Antibody Center, in La Jolla, Calif. Scripps and IAVI scientists will work together at this laboratory center, and IAVI has committed \$30 million in funding over a five-year period. The new facility will complement the capabilities of IAVI's other two research laboratories, the AIDS Vaccine Design and Development Laboratory (Brooklyn, N.Y.) and the Human Immunology Laboratory (London).

Researchers at these labs have become members of the AVC so that there is a tight connection between the IAVI facilities and the geographically disparate consortia. University of Pennsylvania's Doms says, "IAVI is moving to a model in which real centers are embedded in virtual centers. This model will bring an appropriate organizational scale to a difficult problem." The synergy from bringing the new and old AVC components together in this novel multilayer organization can engender shifts in researchers' perspectives. New approaches to the HIV vaccine puzzle may result. That, at least, is the hope in this period when the way forward is still unclear.

By David Gilden

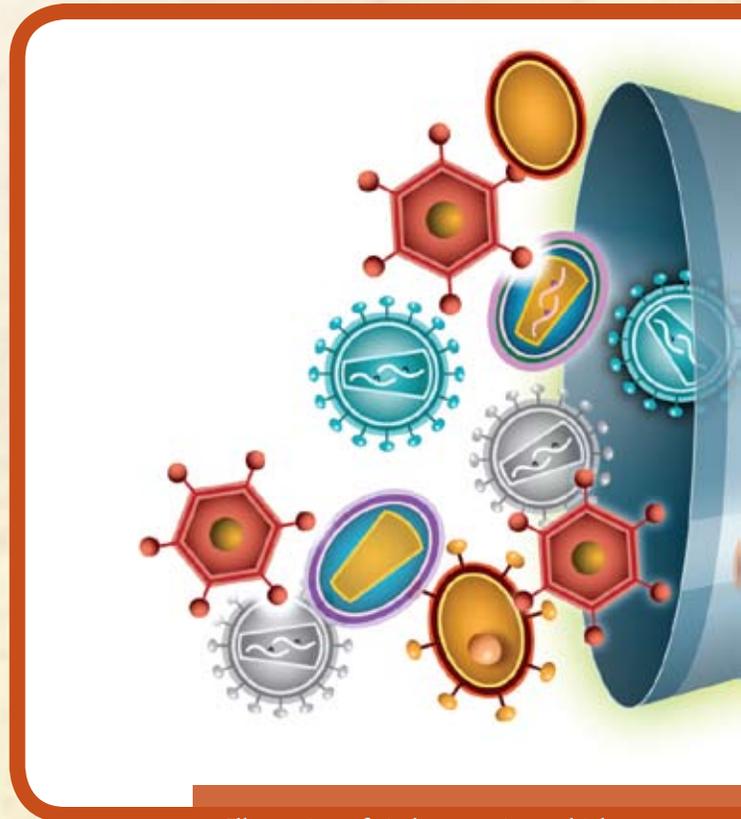


Illustration of viral vectors into which HIV gene(s) have been inserted

Credit: Samuel Velasco/5W Infographics



HIV Vaccine Trial Centers Forge Research Network in Developing Countries



Lessons Learned:

- *With strong in-country leadership, sufficient staff training and infrastructure investment, it is possible to establish HIV research centers in developing countries capable of conducting HIV vaccine trials meeting international standards.*
- *There are a number of epidemiologic and immunologic studies that will contribute to the science of HIV vaccine development and can be conducted at the HIV vaccine trial centers.*
- *The vaccine trial centers can conduct studies of other vaccines or other prevention technologies; this flexibility is important as medical research evolves.*



Pontiano Kaleebu, assistant director of research at the Uganda Virus Research Institute, and colleagues are at the forefront of the AIDS vaccine research program in Uganda.

Photo by Vanessa Vick

An HIV vaccine promises to be the magic bullet that ends the AIDS epidemic. Even a partially effective vaccine could gradually diminish HIV's impact. According to the latest estimates by the International AIDS Vaccine Initiative (IAVI), new infections would decrease by a quarter if a 50-percent effective vaccine reached just 30 percent of the global at-risk population. But any level of vaccine protection has proved elusive despite 25 years of effort.

The long wait has only increased the sense of urgency. This decade has produced a number of vaccine candidates, and IAVI has emerged as a major player in the race for realizing an HIV vaccine accessible to all who need it. By 2000, IAVI was already cultivating connections with academic and corporate researchers to accelerate a pipeline of potential vaccines making their way to human trials. To ensure that such products work, vaccine candidates must undergo human testing in Africa and Asia, where the bulk of new infections occur. Regional factors may require adjustments in the

vaccine's composition. Different HIV subtypes are prevalent, and local differences in immune response may exist due to genetic and environmental factors.

IAVI, for this reason, has developed clinical research collaborations in eastern and southern Africa and in India. Working with local researchers, the organization has helped strengthen clinical research facilities' physical and human resources so that when a promising vaccine candidate is ready, there will be a trial network prepared to test it.

At first, IAVI staff thought that a vaccine could be rapidly pushed to fruition. Pat Fast, M.D., Ph.D., IAVI's chief medical officer recalls, "I started working with IAVI in 2001. We had one person in Kenya. I was told to prepare for efficacy trials in three years. We couldn't just go to a CRO [contract research organization]." Efficacy trials involve thousands of trial participants distributed over a number of locales. IAVI decided to build on the existing resources to rapidly ramp up local trial capabilities. As it turned out, none of the available vaccine candidates performed well



Lab staff throughout the clinical research network are trained in good clinical practices — international standards against which all clinical trials are conducted.

Photo by Jean Marc Giboux/Getty Images

enough in early trials to justify moving them into the more advanced efficacy studies. The network IAVI established nonetheless has proved valuable in gathering the data needed to more efficiently develop and test future vaccine candidates. It has also enabled local investigators to study additional HIV prevention measures. Their research outlook has broadened to include other diseases, as well.

Upgrading Existing Capacity

When IAVI started considering bringing HIV vaccine trials to developing countries, capacity was limited for both conducting clinical trials and performing sophisticated laboratory testing. IAVI's vision encompassed long-term capacity building; it wanted to create integrated trial centers able to do their own lab work and data collection. The goal was to establish a network prepared to do early, small clinical trials at first and then graduate to larger efficacy studies.

In 2001, IAVI sent a survey to about 50 facilities, asking about trial capabilities and local HIV epidemiology. Site visits followed. According to Fast, "The most important thing we were looking for was African leadership. Next was high HIV rate — you have to go where the risk is — and after that came the willingness of the researchers, community and government to work with us."

Infrastructure and staff training were lower on the list because these were "fixable."

IAVI ultimately agreed to partner with researchers at 11 institutions, which became designated as Clinical Research Centers (CRCs). These centers involved partnerships with local research organizations in six countries: Uganda, Rwanda, Zambia, Kenya, South Africa and India. All the CRC facilities except some South African locations needed extensive renovations or new construction. A clinical trial unit has to collect a broad array of health data to check on safety as well as efficacy. It looks something like a modern doctor's office, with a waiting room, exam and counseling rooms, HIV testing facility and bathrooms to collect urine samples. Labs to analyze biological specimens are required to diagnose HIV infection and evaluate vaccine safety. These labs need a standardized set of equipment and external quality assurance systems to assure that results from different trial units are comparable.

This huge organizational effort entailed shipping elaborate, high-tech equipment from distant manufacturers while at the same time working with local contractors. Regulations and construction practices were a little different in each country.

To successfully conduct multi-site trials, the CRCs have to adopt a uniform set of operating procedures. Leslie Nielsen, IAVI's country director for Uganda, notes, "The Uganda CRC staff conduct research in Uganda according to the highest international standards. But the doctors and nurses here treat patients under very difficult conditions and have a heavy workload. In a clinical trial, you need rigorous recording of adverse events and the other data." New medical personnel need education in internationally accepted good clinical practice. Lab staff requires training in good clinical laboratory practices. This training is coordinated by IAVI's Human Immunology Laboratory in London and at the University of the Witwatersrand's Contract Laboratory Services in Johannesburg. Quality assurance testing ensures continued consistency of lab assays across the network.

An intensive education effort also takes place within the communities that provide trial volunteers. Communities need to understand how a vaccine trial operates in addition to basic information on HIV transmission and disease. This information can be conveyed through community meetings and educational outreach materials. To provide informed consent, the actual trial volunteers require much more specific counseling on the details of the study and the risks and benefits they incur, if any. There are also a number of study benefits, as participants receive HIV prevention counseling and testing. When needed, they also receive care and/or referrals for HIV, sexually transmitted diseases, reproductive health issues and basic medical issues. All these efforts, of course, involve training staff in counseling and advocacy skills.

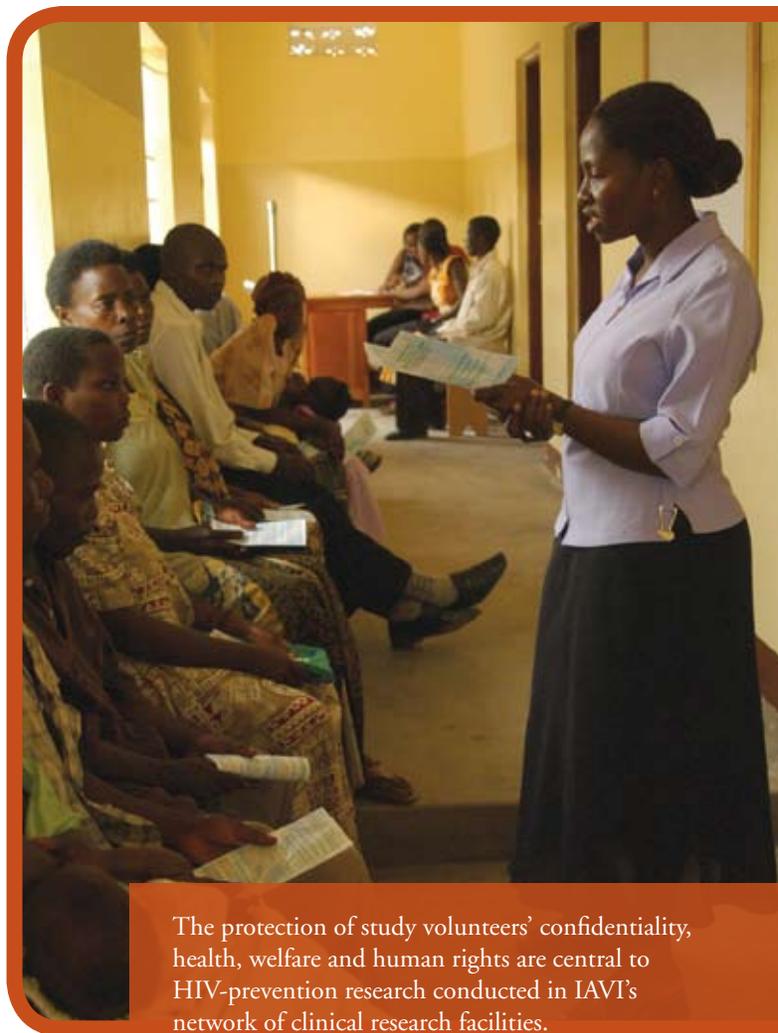
Local personnel directly manage community programs, and they have taken over the scientific activities, as well. IAVI maintains a trial monitor staff to ensure that proper trial procedures are followed. Megan McBride, IAVI's senior director for clinical operations, says, "There's still a lot of communications between IAVI headquarters and the CRCs, with frequent visits. But the centers are now performing at a high level, so they don't need so much supervision or training anymore."

Vaccine Preparatory Studies

With the vaccine pipeline constricted, the CRCs have moved into vaccine preparatory studies. The studies involve tracking HIV incidence in large cohorts so as to identify high-risk populations for future vaccine efficacy trials. Another study evaluates the immunologic and virologic responses in volunteers recently infected with HIV. There are also studies evaluating persons showing possible resistance to HIV: either because they are able to control virus levels over time without antiretroviral medication or appear to be high-risk "exposed but uninfected" persons. These immunologic/virologic studies are useful in determining protective immune responses that an HIV vaccine should trigger or mimic.

The study tracking HIV incidence has had to adapt to an evolving HIV epidemic. Observed HIV incidence has been lower than expected in certain groups, possibly related to extensive counseling and testing programs. The CRCs have enhanced their flexibility by broadening the high-risk populations they recruit. Aside from commercial sex workers, the centers follow discordant couples (in which one partner is HIV-infected and the other is not) and men who have sex with men.

Stigma remains strong against HIV infection and the risk activities associated with it. The CRCs have had to create a safe, non-judgmental atmosphere in which study volunteers from each risk group can feel comfortable. Doing this involves staff with special sensitivity training and the creation of protected meeting places. "The objective is to conduct effective HIV prevention research in an environment of confidentiality and sensitivity to the needs and safety of the study volunteers," says Pauli Amornkul, M.D., IAVI's regional medical director, formerly based in Kenya.



The protection of study volunteers' confidentiality, health, welfare and human rights are central to HIV-prevention research conducted in IAVI's network of clinical research facilities.

Photo by Vanessa Vick



IAVI fosters partnerships with local clinical research centers to build scientific capacity in countries heavily affected by the AIDS pandemic.

Photo by Vanessa Vick

A completed, published study measured standard clinical laboratory values in healthy Africans (see E. Karita et al. *PLOS One* 2009, 4(2):e4401). It analyzed the test results from 2,100 volunteers throughout the trial network to create local standard reference ranges for blood values and organ function. By United States and European standards, a third of these volunteers would have been ineligible for vaccine trials although their test results were within the normal range for Africans.

Individual Research Centers

Kenya: The first CRC collaboration was in Kenya. It expanded to centers in Uganda, Rwanda and Zambia before adding branches in South Africa and India.

The studies in Kenya take place at three locations. Two are in Nairobi and associated with the Kenya AIDS Vaccine Initiative based at the University of Nairobi. One installation is at the medical school, in Kenyatta National Hospital. The second is in the impoverished west Nairobi district Kangemi. It originally made use of converted shipping containers; these have been partially replaced by new construction. Another CRC, on the northern Kenyan coast, is run by the Kenya Medical Research Institute, which, like the University of Nairobi, is a government institution.

The principal investigator in Nairobi, Professor Omu Anzala, Ph.D., recalls the steps that led to his role in initiating the CRC network: “I was doing my postdoctoral work at the University of Oxford’s Institute of Molecular Medicine. My lab was already constructing an HIV vaccine, and IAVI was looking to sponsor trials. We made a proposal to IAVI, and I was given the responsibility to set up trials for the vaccine in Kenya.”

The vaccine in question involved “naked” HIV DNA plus a booster immunization with MVA, a weakened form of the small pox vaccine virus. Researchers genetically modified the MVA booster to produce HIV proteins. IAVI’s original plan was to move this candidate vaccine into advanced human trials after preliminary testing. However, the responses to the MVA and other early vaccines did not appear sufficiently protective, and scientists started working on alternate vaccine designs.

Aside from the stigma attached to groups with high HIV risk, Kangemi and other crowded, poverty-stricken Nairobi districts with high HIV rates have their own stigma arising from a history of violence and lawlessness. Anzala says that the challenging environment has not disrupted his studies. “We started slowly,” he says. “We worked with community groups and educated the community. The community respects us. We have been there eight years, and we don’t have any problems.” The Kangemi facility is also a neighborhood health care resource. It works with a nearby city clinic to ensure that study volunteers receive proper health care, including HIV treatment if they need it.

Rwanda-Zambia: The idea of studying discordant couples comes from Susan Allen, M.D., an Emory University (Atlanta) professor who directs the Rwanda Zambia HIV Research Group. This group’s three CRCs (Lusaka, Zambian copper belt, Kigali) joined the IAVI network in 2003 and 2004. Allen went to Rwanda in 1986. She ran an HIV prevention and research program there until the 1994 genocide. Allen’s group then moved to Zambia, returning later to Rwanda. She became interested in discordant couples during the first Rwanda period, when women in her HIV prevention projects asked her to involve their husbands in counseling.

Allen's latest studies indicate that 80 percent of new HIV transmissions take place within such couples (see K. Dunkle et al. *Lancet* 2008, 371:2183-91). For that reason she has become a prime advocate of couples counseling, a practice that has become a normal procedure in IAVI trials. Allen says, "I would have a problem with any study that didn't include partner counseling. We know the impact. It can increase condom use to 80 percent of sexual acts and reduce heterosexual transmission by at least two-thirds."

The Rwanda-Zambia group identified more than 4,200 discordant couples between July 2003 and December 2005. This population forms a substantial base for the heterosexual transmission study cohort, which IAVI began funding in 2004. The study was following about 1,240 HIV-negative members of cohabiting discordant couples as of April 2009. Researchers check these volunteers' HIV status monthly or quarterly. The cohort feeds into the CRC study of recent HIV infection. The Rwanda-Zambia group is also engaged in vaginal microbicide trials, which can also advance the study of HIV prevention within discordant couples.

Uganda: Uganda contains three CRCs: one established in partnership with the Uganda Virus Research Institute (UVRI) directly and two with UVRI and the U.K.'s Medical Research Council (MRC). UVRI is a long-established research organization dating back to 1936. In 2002, Pontiano Kaleebu, M.D., Ph.D., a highly trained scientist educated in Uganda and the United Kingdom, emerged as the point person for founding a CRC. He became its principal investigator and is now assistant director of research at UVRI as well as head of basic sciences at the MRC/UVRI partnership.

Kaleebu had participated in an earlier Ugandan HIV vaccine trial funded by the U.S. National Institutes of Health (NIH) and was looking for ways to continue HIV vaccine research. Leslie Nielsen, who became the IAVI country director for Uganda, had also been part of the NIH trial's Uganda investigative team. In addition, Jill Gilmour, Ph.D., the head of IAVI's Human Immunology Laboratory in London, had worked in Uganda and was familiar with UVRI. She was able to coach the local lab team in meeting international standards. Nielsen comments, "The university here is excellent. The doctors and nurses are well educated and quite prepared to adopt new methods."

Although the initial team was relatively easy to assemble, physical infrastructure was lacking. UVRI is a branch of the Uganda Ministry of Health, which has preferred to concentrate its scarce funding on treatment rather than research. The CRC started with a vacant piece of UVRI land that was previously a medical waste dump. IAVI had to build from the ground up. It constructed completely new offices, clinic and lab.

The center worked on an early trial of the same Oxford vaccine candidate studied in Kenya as well as a preliminary trial of another type of vaccine utilizing a bioengineered nonpathogenic virus. The CRC network meanwhile expanded to include two Uganda facilities operated by the MRC (one at nearby Entebbe Hospital and the other in Masaka on Lake Victoria). They conduct the CRC vaccine preparatory studies, such as the large HIV incidence cohort. Borrowing the idea from the Rwanda Zambia group, they are now recruiting discordant couples in an effort to find a population with high HIV incidence. Lake Victoria fishing communities are a new high-risk population being recruited.

Anatoli Kamali, M.D., principal investigator at the Masaka CRC facility, observes that the inability to move on to advanced vaccine trials has been frustrating, but "keeping up momentum has been easier than expected. We should not get distracted from our goal." Kamali suggests broadening the CRC collaboration to include pharmaceutical companies that are developing HIV vaccines. "That way, we will be among the first to test them," he says.

The UVRI laboratory has received funding from the Bill & Melinda Gates Foundation's Collaboration for AIDS Vaccine Development and is now concentrating on basic science. One study that Kaleebu has organized tests a new gene expression assay ("microarray analysis") as a way of predicting vaccine response.

The Benefits of International Collaboration

The UVRI CRC's ability to conduct new basic science studies on its own is one example of the benefits emerging from the collaboration. IAVI helped the CRC researchers in the beginning, but now those researchers are the sources of ideas for new vaccine designs while keeping the trial organization ready for the time when efficacy trials are again opportune. As Anzala in Nairobi put it, "Even if there is no vaccine trial, we can study the mysteries of HIV, and that, in turn, will help in developing vaccines. We also want to put the infrastructure to good use by diversifying. We can test TB and malaria vaccines. Everyone has heard this is an excellent unit that can do more."

The CRCs have also blazed the political and regulatory pathways needed to move future trials ahead quickly. It took Anzala's group 18 months to get approval for its first vaccine trial. The Nairobi CRC then worked with the Ministry of Health to streamline the process. The two organizations sponsored a national stakeholders' meeting in 2004 that established guidelines for vaccine research. The meeting also led to an accelerated system for approving new trials. Now a national vaccine protocol review committee submits recommendations to the two ministry of health regulatory boards that oversee pharmaceutical research.



Advancing vaccine design by investigating the intricacies of HIV is critical to accelerating AIDS vaccine progress.

Photo by Vanessa Vick

The Ugandans, too, work to impart a sense of urgency to the country's political structure. UVRI initially took advantage of its high standing in the Ministry of Health to secure government support for the CRC. IAVI CEO Seth Berkley ultimately met with Uganda President Yoweri Museveni, and the two wrote a letter to the Group of Eight (G8) appealing for more HIV vaccine funding.

UVRI continues to give health officials and members of parliament regular updates on HIV prevention technology. The meetings allow the officials to comment on the research agenda. Their comments can result in adjustments to the way research is conducted. These interchanges preserve the government's commitment to Uganda's leading role in vaccine research. In Kenya and elsewhere, this commitment smoothes over bureaucratic barriers. It also results in various kinds of material assistance, such as providing space for study centers or medical care to study participants.

Government support is not to be assumed, and its absence can prove disastrous. When Allen started in Rwanda in the 1980s, the government forbade her from publishing results. It feared that publicizing the nation's HIV problem would drive away investors and tourists. Then the government-promulgated 1994 genocide resulted in the deaths of half the Rwanda project's research staff plus the disappearance of hundreds of the cohort members. The

new government in Rwanda, however, has been very supportive of HIV vaccine and other prevention research. Despite that support the CRCs in several countries face challenges recruiting men who have sex with men into cohorts due to stigma against homosexuality.

Work on the community level helps to protect against the capriciousness of national politics. As described, considerable time is spent on public education so that residents understand and cooperate with the studies taking place in their locales. Also, each Clinical Research Center has a community advisory board, established with IAVI's guidance. Some have gender advisory boards or work with peer leader networks.

These types of local organization have broader effects: They combat HIV stigma and homophobia by providing a sense of empowerment. As the community boards and networks gain experience, they seek to advise government officials on policy matters. In this way, there emerges a grassroots constituency for scientifically sound, ethical HIV vaccine research. This constituency's existence ultimately will engender greater appreciation of medical research and health care in general.

By David Gilden

Making New Medical Innovations Available in Developing Countries First, Where They're Needed Most



Lessons Learned:

- *Product development partnerships (PDPs) have a growing role in addressing scientific and technical challenges.*
- *Negotiate licenses with private industry to allow resource-constrained countries widespread access to new, approved prevention technologies and use in future combination therapies.*
- *When possible, conduct clinical trials in developing countries that have higher disease burden.*
- *Make use of regulatory mechanisms in developed countries that offer advisory opinions on medical products for global public health application.*



An IPM employee works on a ring press at the Clinical Trial Material Facility in Pennsylvania, where materials for IPM's clinical trials are manufactured.

Photo by Andrew Loxley, Felt Photography

While cutting-edge medical innovations may ordinarily be applied in wealthy nations before they trickle down, if ever, to poorer countries, the opposite to this rule may occur if one product development partnership (PDP), the International Partnership for Microbicides (IPM), succeeds in developing safe and effective products for prevention of HIV/AIDS.

IPM, a nonprofit whose donors include the Bill & Melinda Gates Foundation, 12 governments in North America and Europe, and several international organizations, hopes to create microbicides — products to be used vaginally by women — that will help to prevent the transmission of HIV. These products are based on a number of experimental and approved therapeutic drugs that have been charitably licensed to IPM by private industry. Several pharmaceutical companies have made active compounds available beginning in 2004 with Johnson & Johnson's license to IPM for

dapivirine, and with one of the latest being Pfizer, which licensed its approved AIDS therapeutic maraviroc to IPM early in 2008. IPM has not yet gotten a microbicide approved, but human clinical trials of dapivirine are under way, with trials of a product containing maraviroc scheduled to begin next year.

Why a Microbicide?

Part of the motivation in developing microbicides is to create a method of AIDS prevention that women can initiate, unlike condom use, over which men have the most control. “Women in these settings have so little control over their own reproductive health, that this represents one of the best options to them,” says Joseph Romano, Ph.D., executive director of research and development at IPM.

To date, IPM's commercial partners have agreed to royalty-free licenses of their technology for distribution only in developing



The fundamental purpose of microbicides and the clinical trials process is keeping women healthy and safe. Here, a study nurse demonstrates a screening exam at the International Centre for Reproductive Health in Mombasa, Kenya.

Photo by Geoff Oliver Bugbee

countries, where women carry a higher portion of the burden of HIV than in resource-constrained countries, according to IPM.

If one or more active compounds are successful in preventing transmission, IPM is exploring a variety of product formats to fit a woman's convenience. "Our goal is to have multiple dosage forms. IPM is actively investigating the development of various kinds of vaginal rings designed for sustained release over 28 days, as well as gels, tablets and films designed for once-a-day use," Romano says.

Why a Product Development Partnership?

Although from a legal standpoint IPM is a partnership only in name, it is one of a class of organizations known as "product development partnerships" (PDPs) featuring public-private cooperation to overcome thorny medical issues. These PDPs are intended to bring together the resources and expertise of nonprofit global health organizations with the proprietary drugs and technology developed by for-profit pharmaceutical companies.

"Partnership' is part of the name of the organization and an important aspect of how the organization operates, but in form it's a not-for-profit corporation," says Paul Model, J.D., attorney for IPM, who helped negotiate its licenses. Established in 2002, IPM

is funded by foundations, international organizations and national governments, including Canada, Ireland, the Netherlands, the United Kingdom and the United States among others.

"The notion is that in a larger sense the nonprofit sector and for-profit sector are becoming partners in the development of drugs for neglected diseases or drugs that would not get developed for commercial reasons," Model says, adding that other PDPs are working on malaria, tuberculosis and a variety of tropical diseases.

"By their very nature, PDPs are self-selecting for addressing some of the world's most difficult technical problems," says Mark Mitchnick, M.D., an IPM consultant who was chief science officer for the company during its formative years. "As an example, there have been very few commercial efforts to develop a microbicide. Nobody starts a PDP to look at cardiovascular disease, because ample resources are being devoted to address that problem. A microbicide would be a first-in-class drug, because there never has been a product (other than condoms) to prevent HIV, such as a microbicide. These become very daunting ventures scientifically," he says.

While Pfizer is one of IPM's most recent industry partners, it was Johnson & Johnson subsidiary Tibotec that enabled IPM to begin

its development program, by stepping forward and licensing its experimental drug dapivirine in 2004. “The drug has been evaluated in multiple clinical trials for safety and pharmacokinetics in a gel and vaginal rings, in Phase I studies,” says Romano, adding that the formulations have been tested in more than 200 people. The microbicide formulations are expected to go into expanded human trials in the United States and Africa in 2009 and 2010, and Phase III trials are scheduled for 2011.

Why do pharmaceutical companies license their drugs to IPM? In some cases, both senior management and product development scientists within the pharmaceutical company itself realize the potential for their drug to make a significant difference in the lives of people in resource-poor settings. While development of products for these uses may not be consistent with a pharmaceutical company’s economic model, many pharmaceutical executives and scientists are nonetheless concerned to make these products available to populations in need. They will take the initiative to identify potential nonprofit licensing partners with the capacity to take a product through to licensure.

In other cases where PDPs approach industry for their drugs, the potential for improving a company’s public image is an important incentive. Charitable licenses between pharmaceutical companies and PDPs can garner significant positive public attention for both parties. In addition, pharmaceutical executives understand that microbicides are very different products from the therapeutic agents sold in the developed world, so there is less reason to worry about the potential negative impact that a charitably licensed product might have on the profitable markets in which the pharmaceutical companies operate.

Another potential drug is tenofovir, an approved AIDS treatment therapy made available by Gilead, which also has a very good human safety database, according to Romano. In addition to these two drugs, and maraviroc, which was U.S. Food and Drug Administration approved about a year-and-a-half ago, other drugs have been licensed by Bristol-Myers Squibb and Merck, all of them experimental.

A threshold level of trust is essential in establishing relationships with industry partners. “Getting Tibotec to allow IPM to work with its compound in a relatively unrestricted way was enormously important,” Model says. “The Tibotec license originally contemplated a fairly formal structure of governance that included the establishment of a committee that would meet regularly and compose a set of rules for the conduct of the development effort. This formal governance structure has become less important as the development project has progressed. Once the two sides got to know each other pretty well, less formal communication turned out to work well from the perspective of both sides,” he explains. (See sidebar on negotiating PDP licenses.)

Pearls and Pitfalls in Negotiating PDP Licenses

IPM attorney Paul Model says the organization has made strides in learning how to negotiate beneficial license agreements with the pharmaceutical industry. “IPM now has something a lot closer to a standard form than it did in the beginning,” Model says.

A beneficial aspect of the license agreements that IPM has sought in negotiations is getting an identical list of countries in which IPM could distribute an approved microbicide. “Stapled to the back of each license is the same list of about 100 countries. This means that IPM will not be in a situation where it can use one licensed compound in a particular country, but cannot use another compound in the same country,” he explains.

The license agreements permit IPM to combine active pharmaceutical ingredients in case it is a combination product that ultimately proves most effective as a microbicide. “As a matter of fact, the license for one of the compounds contemplates that it will only be used as part of a combination product. IPM and others in the field believe that the likelihood of ultimate development of a combination product is high.”

Another aspect of the license agreements that requires considerable attention is the balancing of the industry partner’s concerns about the appropriate use and development of an active compound with IPM’s needs for the freedom to innovate. “In the maraviroc license, for example, the tension is really between IPM’s desire to innovate and Pfizer’s desire to maintain control over maraviroc,” says Model.

One way this tension was resolved was through negotiations over access to the compound and arrangements for supply. IPM is a virtual development organization that uses a lot of contractors. The maraviroc license includes rules and procedures about access to maraviroc for partners and contractors providing development services to IPM. These rules and procedures include standard terms for allocation of intellectual property rights among IPM, Pfizer and third-party contractors, as well as procedures for review of the contractors themselves. IPM and Pfizer also negotiated detailed terms for supply and manufacture of the active compound.



A priority for studies is that people living in the community fully understand the research activities conducted there. This community mobilizer works with *Projet Ubuzima* — an International Partnership for Microbicides sponsored research center in Kigali, Rwanda — to educate community members about clinical trials.

Photo by Geoff Oliver Bugbee

The more recent license of maraviroc by Pfizer was remarkable because the license was granted in the context of the FDA approval obtained by Pfizer for marketing maraviroc as a treatment for HIV infection. The results of IPM's preclinical and clinical studies of maraviroc, as well as IPM's efforts to obtain regulatory approval, could potentially have an impact on the status of maraviroc as a therapeutic, a matter in which Pfizer has made a very substantial investment. A crucial factor in the collaboration was building Pfizer's confidence in IPM's ability to undertake drug development in a professional manner and in IPM's understanding of Pfizer's needs and drug development generally.

"It was about a year before IPM signed the license agreement that Pfizer began providing IPM with small batches of the drug for a shorter period of time under a material transfer agreement," Model says. "This allowed important formulation work to get under way

before the agreement was actually formalized, thus speeding the overall product development process."

In Case of Success

The challenges in making a microbicide effective for the prevention of HIV include not only the development of a safe and effective product, but also making access to that product in resource-poor countries a reality after the product has been developed. IPM has already put some thought into access issues.

In part, some of the preparation associated with access has already gone into IPM's clinical trials strategy. "Women in the U.S. and elsewhere are typically tested in Phase I and II studies. However, Phase III efficacy studies have to be done in areas where the HIV levels are high enough that if we introduce interventions like microbicides, we can see reductions in the number of infections. Infection rates are not high enough in the developed world for efficient clinical research purposes," Romano explains.

The ultimate question as to clinical trials comes down to what country will regulate an approved microbicide. "Our goal is to have approval with an agency like the FDA or Europe's regulatory body, the [European Medicines Agency] EMEA. One of our interesting options would be to apply under Article 58 of the EMEA. This would involve engaging in a process by which the EMEA doesn't per se approve a product, but scrutinizes it from the same level it would from an approval perspective, and then offers its opinion to other regulatory bodies, particularly in the developing world. This was designed to benefit public health in the developing world," he adds.

Pricing the ultimate product is another matter. "IPM itself will never make a profit off of this, but the issue is that a microbicide would still cost something to make, and there would still have to be funding coming from some source," Model says. Cost considerations are an important issue in negotiating license agreements with pharmaceutical companies. These agreements give IPM the right to manufacture and distribute microbicides in developing countries so that the costs of the product will be kept as low as possible.

"We'd like to make an inexpensive gel, in which the most expensive component is the applicator itself. The gel and the drug inside the gel would cost in the pennies range to manufacture," Romano says. "In vaginal rings, we know you would only need 12 rings per year for a woman to be protected since the product would be used monthly, and if that's cheaper than it costs to manufacture 30 individual daily doses of a gel product, that would be great. On the other hand, vaginal films would be very inexpensive to manufacture and don't necessarily require an applicator," he adds. In addition, the film, which fully dissolves, has the advantage of being less of an environmental burden.

Another major challenge contemplated by IPM is how the microbicide would be manufactured. While the biggest cost IPM is thinking about in the foreseeable future is that of doing clinical trials to demonstrate that a product works, the focus may change dramatically in the event of a success.

“At the moment IPM is producing product on a small scale, in order to conduct Phase I and II trials, at a manufacturing facility in Bethlehem, Pennsylvania,” Model says. “If IPM succeeds, the scale of manufacturing will go up by orders of magnitude. At the moment IPM is performing trials in tens or hundreds of women. If you assume that 10 million women in Africa would be receiving a successful ring product for monthly use, 120 million rings a year would need to be manufactured,” Model explains.

“IPM has already thought extensively about local manufacturing in South Africa, for example. Governments in the developing world may be very interested in promoting this product,” he adds. IPM’s plans for manufacturing for clinical trials and initial product launch include solicitations of interest from manufacturers in Europe, Asia and Africa. Fortunately, compared to costs for manufacturing of vaccines, investments in microbicide manufacturing scale-up are relatively low and will likely be borne by IPM’s new and existing donors.

Potential Earnings

While IPM’s license agreements don’t permit the PDP to sell any approved microbicide in developed countries, it is an open question as to whether a successful product would find a ready market in countries like the United States and in Europe.

“IPM’s mission is focused on less developed countries. Whether a pharmaceutical company partner is going to be able to market an IPM microbicide product in the industrialized world will partly depend on what other patents or intellectual property might be involved. For example, suppose that IPM develops a combination product that has two compounds in it. Let’s say the product includes Pfizer’s compound and Tibotec’s compound. Pfizer can’t just go out and sell that product in the United States and Europe, because they’d have to get the right to the Tibotec compound first,” Model explains.

In general, pharmaceutical companies have agreed to defer these negotiations until a product has been shown to be safe and effective. Since almost all of the microbicide development costs are borne by the PDP (and its donors), and the size of the market in the developed world is unclear, there is little financial risk to a pharmaceutical company in postponing these discussions.

In either case, if a successful microbicide were marketed in developed countries, earnings could result. “If, for example, Pfizer marketed an IPM microbicide under the arrangements called for in the maraviroc license, IPM would be entitled to a royalty. It could be appropriate to try to recover some of the investment made by IPM’s donors, although earning a royalty is not a priority for IPM and should not get in the way of the core mission of making safe and effective microbicides available to women in developing countries,” Model says.

By John Otrompke, J.D.



During the site development process, clinics, laboratories, pharmacies and offices all take shape where there were none before. Here, a lab technician works at the Kilimanjaro Christian Medical Centre in Moshi, Tanzania, an International Partnership for Microbicides-supported research center.

Photo by Geoff Oliver Bugbee

Product Development Partnership Aims to Develop First Vaccine Against Malaria Parasite



Lessons Learned:

- *Maintaining close collaboration and ongoing communication among project partners is critical.*
- *Robust systems (financial, management, etc.) are needed to enable the conduct of complex clinical trials across multiple centers.*
- *Ongoing support for capacity-building at study centers, including helping to ensure capacity for crisis communications planning and media relations at trial sites is of primary importance.*
- *Flexibility — being able to respond effectively and adapt to unanticipated developments or findings — is essential during the ever-changing testing phase.*



Photo by Shutterstock® Images

Malaria kills close to a million people every year and sickens many millions more. Most of the casualties of this disease are young children under the age of five living in sub-Saharan Africa. In an effort to stem deaths from malaria, the PATH Malaria Vaccine Initiative (MVI) has collaborated with GlaxoSmithKline Biologicals (GSK Bio) to evaluate the RTS,S malaria vaccine candidate. This is thought to be the first full vaccine development collaboration between a product development partnership (PDP) and a large pharmaceutical partner. However, that is not the only “first” designation with which the project is likely to be labeled.

“If we are successful with RTS,S, not only will it be the first vaccine against malaria, but the first against a human parasite,” says Christian Loucq, M.D., director of MVI, a program of the nonprofit organization PATH.

RTS,S is the first malaria vaccine candidate to ever reach large-scale Phase III clinical testing, typically the most critical of the last steps

before licensure. This Phase III study is designed to confirm and more precisely, determine the efficacy as well as confirm the safety of the vaccine.

Developing the first-ever vaccine against a human parasite has proven challenging. “The development of RTS,S has taken longer than that of an average vaccine, which is about 10-15 years, but RTS,S will be the first vaccine against a human parasite,” explains Joe Cohen, Ph.D., the co-inventor and one of the original patent holders for RTS,S, who is also vice president of R&D for Vaccines for Emerging Diseases and HIV at GSK Bio. “This groundbreaking scientific achievement cannot be overstated, because it required scientific breakthroughs, particularly in the fields of genetic engineering and immunology and even a new clinical testing infrastructure.”

RTS,S was created in 1987 by GSK Bio, the vaccine division of GSK, in close collaboration with the Walter Reed Army Institute of Research. In 2001, with support from the Bill & Melinda Gates Foundation, PATH and GSK entered into an agreement to

Steps in Malaria Vaccine Development

Research and preclinical development: Identify relevant antigens and create vaccine concept, preclinical evaluation, develop vaccine manufacturing process.

Phase I clinical trials: Preliminary evaluation of the safety profile and immune response in malaria-naïve and malaria-exposed populations.

Phase II clinical trials: Monitor safety and potential side effects, measure immune response, evaluate efficacy against infection and clinical disease, and determine optimum dosage and schedule.

Phase III clinical trials: Continue to monitor safety and potential side effects, and evaluate efficacy on a large scale.

Submission to regulatory authorities: Submit vaccine application to regulatory authorities for approval to market (i.e., licensure).

Introduction: Make vaccine available for use.

Phase IV trials: Conduct post-marketing safety monitoring; answer outstanding research questions.

develop the vaccine for infants and young children in the sub-Saharan Africa region. Today, clinical development of RTS,S is led by the Clinical Trials Partnership Committee, a consortium of leading African research institutions, MVI and GSK Bio. The Gates Foundation continues to fund the vaccine candidate's clinical development through grants to the PATH program.

“This project demonstrates the importance of collaborations and partnerships,” says W. Ripley Ballou, M.D., deputy director for Vaccines, Infectious Diseases Development, Global Health at the Gates Foundation. “Since the vaccine has never been commercially attractive, it required government labs to take an interest and then for a multitude of partners to bring specific skill sets to bear or it simply wouldn't have happened.”

The RTS,S vaccine is a recombinant protein that couples part of the *P. falciparum* circumsporozoite (CS) protein with the hepatitis B surface antigen in a proprietary GSK adjuvant system. As a result of its design, the vaccine protects the human liver against both the malaria parasite and hepatitis B, a severe form of hepatitis that can lead to liver disease, liver cancer and death.

Development of a Groundbreaking Partnership

Clinical evaluation of RTS,S began in 1992 in adults in the United States and Belgium and was followed by a trial in more than 2,000 children in southern Mozambique in 2003. In total, seven Phase II pediatric trials were conducted in Africa. Findings of the 2003 trial showed RTS,S to be effective for a minimum of 18 months in reducing clinical malaria by 35 percent and severe malaria by 49 percent. Data from a more recent study showed a 65 percent reduction in first malaria infection (or 65 percent protection against risk of infection) in infants over a six-month follow-up period.

“The RTS,S vaccine candidate had demonstrated proof of concept, thereby warranting further clinical development, at a time when no other candidates had advanced as far,” says Loucq. “Over the next several years, RTS,S continued to demonstrate that it was safe and sufficiently efficacious to warrant moving to the next stage of development — now including the start of a large-scale, Phase III trial in sub-Saharan Africa.”

Throughout the history of the partnership, Ballou and Cohen have been key figures in the vaccine's development. Their paths crossed many times, first as collaborators and then as colleagues.

As a key member and eventually leader of the U.S. Army's malaria vaccine research team at Walter Reed, Ballou oversaw the development and testing of more than a dozen vaccine candidates that led, in collaboration with scientists at GlaxoSmithKline, to the creation of RTS,S. Before Ballou retired from the U.S. Army in 1999, he was instrumental in the creation of the Malaria Vaccine Initiative at PATH and wrote elements of the original funding proposal. Ballou's career path included five years at GSK Bio in Belgium, working on the vaccine, and finally in April 2008, he joined the Bill & Melinda Gates Foundation.

Cohen left academic research in 1984 to join the vaccines division of GlaxoSmithKline (then SmithKline-RIT). Three years later, Cohen took over the reins of the company's Malaria Vaccine Program. Scientists at GSK and Walter Reed had been working on a vaccine based on the circumsporozoite protein, but the initial effort had not resulted in a stable, immunogenic and efficacious vaccine.

The years spent working on RTS,S have been grueling and often unkind. “You have to be prepared for the failures as well as the successes,” says Ballou. “The first six years of the efforts toward developing RTS,S were a series of bitter disappointments and discouraging news. Indeed, a lot of people did walk away but, overall the RTS,S project has been blessed with leaders undaunted by failure.”

Cohen and his team thought they could stabilize the vaccine and increase its immunogenicity by fusing the CS protein to a form of the recombinant technology found in GSK's successful hepatitis B vaccine. When the team added GSK's proprietary Adjuvant Systems, the immune response was even better. Cohen and his colleagues have since spent more than two decades perfecting and building upon this fundamental insight.

Structuring the Partnership

The first agreement between GSK and PATH was finalized in January 2001. This collaboration has involved three iterative, major milestone-driven agreements between the two organizations:

- Initial clinical development agreement: Project initiation through Phase II proof of concept (2001-2004)
- Collaboration agreement: Phase II and Phase III development programs, including establishment of supply and pricing terms (2005-2009)
- Amendment of 2005 collaborative agreement (2009-2014)

Each phase of the collaboration has taken approximately a year to negotiate. Ongoing maintenance of the partnership requires a significant investment of time from both partners.

The two partners bring a range of capacities required for a vaccine development project. However, one organization will typically bring a greater depth in the areas where it leads. In this partnership, GSK Bio leads on applied R&D (recombinant protein and adjuvant systems technologies); clinical protocol development; clinical trial operations; regulatory affairs; and process development, scale-up, and large-scale manufacturing. MVI leads on African trial-site relations, contracts, and capacity building; crisis communications planning and media training for study center investigators; planning for decisions on vaccine use in African countries; and management and oversight structure for the project.

To ensure steady and productive progress, the project has three formal management and oversight structures:

- MVI-GSK Bio Steering Committee contractually defined as the decision-making body for the partnership
- Commercialization, Policy and Advocacy Working Group, a Forum for joint discussion of issues around translating the vaccine into an intervention delivering public health impact. This body is chartered by and reports to the Steering Committee.
- Clinical Trials Partnership Committee (CTPC), which includes GSK Bio, MVI and investigators who address protocol and other issues related to the Phase III trial and ancillary studies.

The establishment of the CTPC reflects the importance of the African study centers involved in the Phase III trial, each chosen for its track record of world-class clinical research, strong community relations and commitment to meeting the highest international ethical and regulatory standards. Relationships with the study centers are also governed by contractual agreements, with a separate agreement among MVI, GSK and each study center. The CTPC is now represented on the RTS,S Steering Committee, which initially only included GSK Bio and MVI.

"The Clinical Trials Partnership Committee (CTPC) is up and running, has effective governance structures (including one or more working groups) that meet regularly, is a route for information sharing and has successfully facilitated some decision-making," says Loucq.

Partnering to Conduct the Phase III trial

Based on the successful trials to date, GSK, MVI and leading African research institutions are continuing clinical trials in infants and young children, the most vulnerable groups and those who would benefit most from an effective malaria vaccine.

A large-scale Phase III multi-center efficacy trial in both infants and in young children was launched in May 2009. This Phase III study is designed to further and more precisely determine the efficacy and confirm the safety of the vaccine in the target population. The RTS,S Phase III trial will be conducted in 11 sites in seven African countries, namely Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and Tanzania, pending required local and national approvals. This trial, which will enroll up to 16,000 infants and children, is expected to become the largest malaria vaccine trial to date. If all goes as expected, the RTS,S vaccine candidate could be submitted to regulatory authorities as early as 2011.

The Phase III protocol was developed with input from all the partners in the trial (all members of the CTPC) and from regulatory authorities such as the European Medicines Agency and the World Health Organization (WHO). Each study-country has undertaken independent reviews to ensure the trial meets national safety, ethical and legal standards for medical research. In addition, there is an independent data and safety monitoring board for the full trial and a local safety monitor will be deployed at each site.

The RTS,S project has built trial capacity throughout Africa that will greatly aid the testing of other vaccines and the distribution of RTS,S, once licensed. This capacity building extends beyond physical infrastructure (such as buildings and equipment) and training directly relevant to the conduct of the trial, to strengthening the skills and abilities of study centers in the financial, management and communications arenas.

Examples of capacity building include collective activities, such as bringing together two personnel from each site (typically, the site principal investigator and the administrator) for a three-day financial management training facilitated by MVI, as well as one-on-one endeavors, where MVI identifies a training need during a site monitoring visit and follows up with a capacity-building visit tailored to address the specific areas of need. Whenever possible, best practices are shared across sites to take advantage of local expertise. On the communications front, MVI has worked closely with trial sites to ensure their readiness to address potential crisis situations and provided training on how to work more effectively with local and international media.

“The key to the collaboration’s success thus far has been, on the one hand, the care with which the study centers were chosen and, on the other, having a common goal: clinical development of RTS,S to the highest ethical and professional standards,” says Loucq. “Regular communications, a spirit of mutual respect and regular face-to-face meetings have helped strengthen relationships and made working together easier, even if it is sometimes challenging.”

It is important to remember both the roles of the partnering organizations and of the individuals that power them. “This project is highly dependent on people; the tremendous effort put forth by each and every participant comes more from the heart than from any hope of fame,” says Ballou. “There’s a lot of work left to be done and many of the people involved have dedicated their lives to seeing it through.”

Paving the Way for Access and Future Vaccines

In addition to their work on clinical development of RTS,S, MVI and GSK began collaborating in 2005 to foresee and address potential bottlenecks in the pathway to introduction, another example of the partnership’s efforts to accelerate the development process. To this end, the partners worked to reach a shared vision for RTS,S implementation in order to align subsequent activities:

To ensure that robust evidence and financial resources are available to all countries in sub-Saharan Africa, allowing each to take a decision if they want to adopt, defer or not adopt RTS,S into their [expanded program on immunization] EPI and/or wider health systems, within one to three years of legal and physical availability.

Among the activities born of this approach is one led by MVI, in collaboration with GSK, WHO and other partners, to map the pathway for a first malaria vaccine through policy, financing, regulatory and procurement bodies into developing countries.

Another critical activity was the partners’ work with WHO to determine the optimal formation, presentation and packaging characteristics so that RTS,S would be able to integrate as smoothly as possible into African health systems. And finally, WHO and MVI began assisting countries to put in place the processes and mechanisms required to facilitate early decision-making around vaccine use (or non-use). This latter effort reflects a recognition that the first malaria vaccine may yet fail, but that early planning is necessary to ensure that if RTS,S is successful, it won’t be left sitting on the shelf, unused.

“Malaria vaccines have little or no potential in the developed world market: There are no wealthy buyers,” notes Loucq. “We have to help ensure that everything that can be done is done to support countries in making and implementing their own decisions around vaccine use.”

And while the work of the partnership extends well into 2014, MVI already has a next-generation vaccine in its sights, according to MVI’s leadership.

“We all hope that RTS,S will succeed in the Phase III trial, paving the way for full introduction as early as 2014. At the same time, we hope to build on the success of RTS,S, finding ways to reinforce the mechanism by which RTS,S works,” explains Loucq. “We are already working on next-generation vaccines, including combination vaccines and other approaches, toward developing a vaccine with greater than 80 percent efficacy by 2025.”

Indeed, new vaccine development is enhanced by the lessons learned from the RTS,S development process. “There is no clear line from one vaccine’s development to another, but rather a mutually reinforcing process whereby the development of one informs another and vice versa,” says Cohen. “This is particularly evident with RTS,S, which has directly benefited from earlier GSK experience and innovations, such as the hepatitis B vaccine and Adjuvant Systems.”

Further, an all important trials capacity is now in place that will greatly aid the testing of other vaccines and the distribution of RTS,S, once licensed. A network of clinicians and scientists is now in place as a result of putting these RTS,S trials, including the Phase III trial.

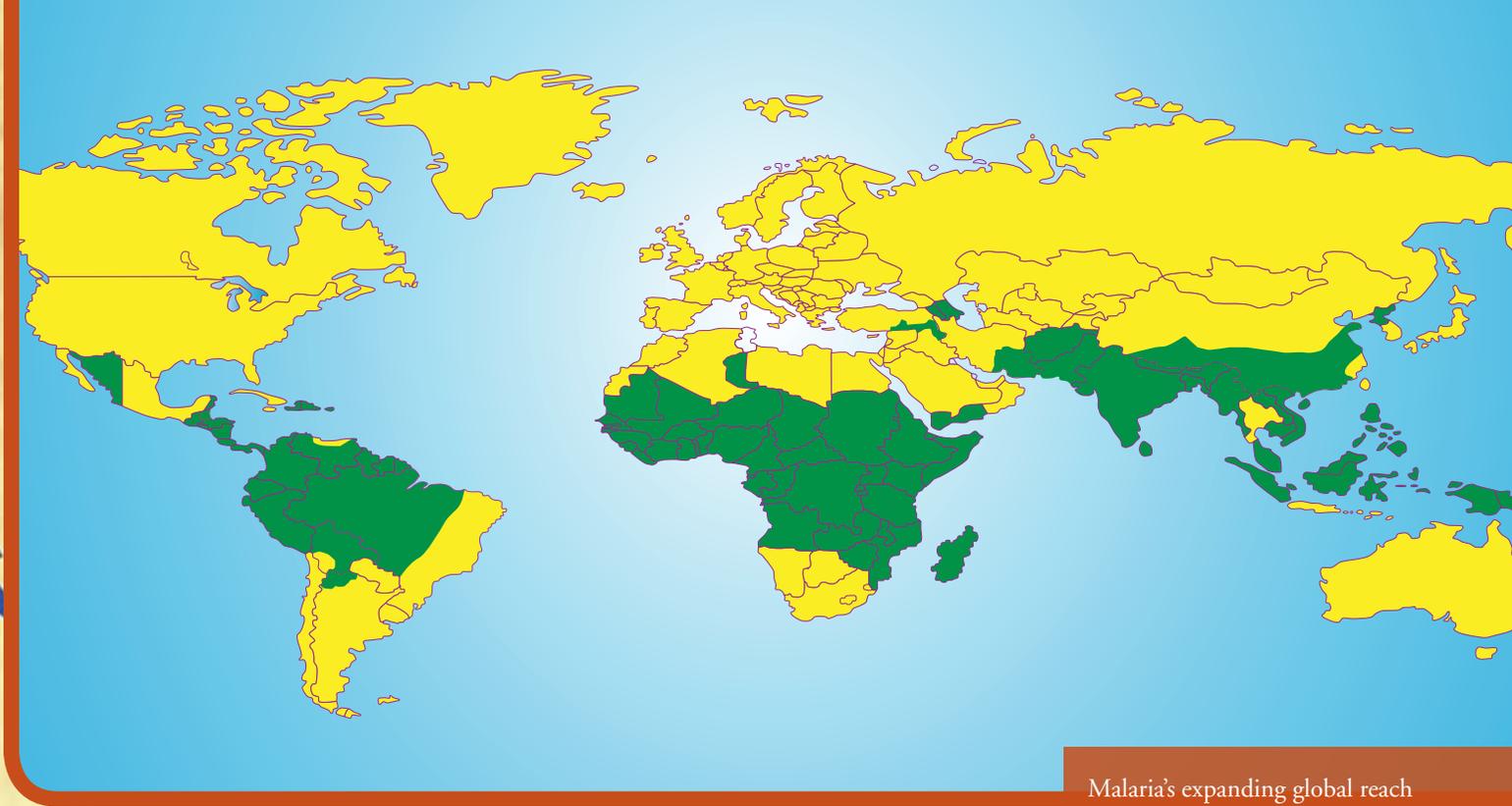
By Pam Baker

Historic Confluence Promotes Malaria Breakthroughs



Lessons Learned:

- *Partnerships between organizations with different but complementary capabilities and strengths are essential to meeting the challenges of an evolving parasitic disease. Independent players cannot make the same progress working alone.*
- *The long-term effort requires both the initial commitment of time, money or resources from management, as well as the motivation and coordination of staff working at all levels.*
- *Creative financing as well as incentives for those involved can help accelerate efforts by making it financially feasible to invest large amounts of money and resources into the effort.*



Malaria's expanding global reach

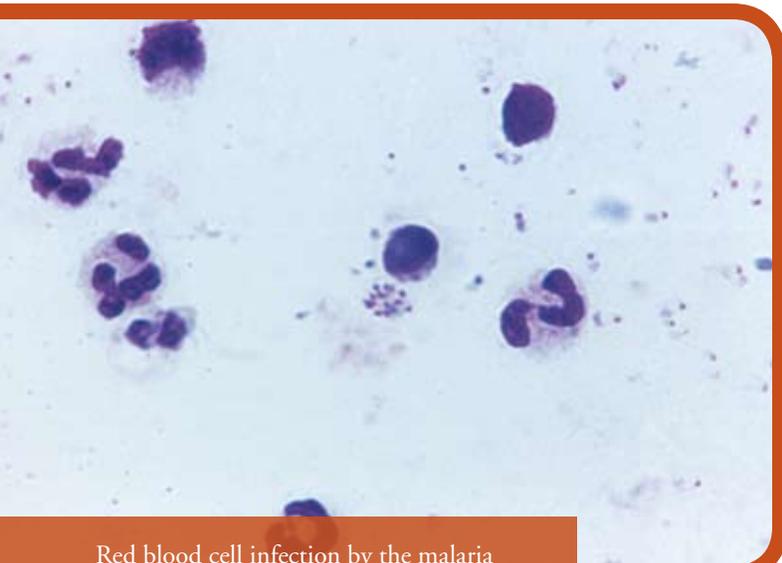
Photo by Shutterstock® Images

Malaria is an ancient red blood cell-encroaching parasite that has seen species come and go. There are specific malaria protozoa for lizards, birds, rodents and, finally, higher primates. The most widespread and virulent form of human malaria, *Plasmodium falciparum*, is 100,000 years old. But malaria as a human scourge did not take off until the advent of agriculture, about 10,000 years ago. From that point on, the spread was supported by the expansion of conditions favorable to the mosquitoes that carry the plasmodium parasites. In some parts of Africa, residents are exposed to malaria through mosquito bites nearly every day. Malaria kills about one million Africans a year, mostly children and pregnant women. The disease is also prevalent in large parts of Asia and Latin America (see map).

The United States and European countries succeeded in eradicating malaria after World War II. These were the easy places, where cool temperatures for large parts of the year limit replication by both the mosquitoes and the parasites they harbor. With the end of DDT-based mosquito control efforts in the late 1960s, the stage was set for resurgence in tropical countries. Countries that previously eradicated the disease, including the United States, are at risk for a return. The mosquito carriers are still present in those countries, and there is a small but steady stream of infected travelers bringing the disease home.

Lacking assiduous mosquito control, the only line of defense against malaria is treatment, and the parasite is notoriously prone to develop drug resistance. Inadequate treatment has led to widespread resistance to current malaria treatments. The only exception is the new combination therapies that include artemisinin compounds derived from a type of wormwood. These relatively expensive regimens too are susceptible to parasite resistance, however. Citing recent reports, Tim Wells, chief scientist for the Medicines for Malaria Venture concludes, "Artemisinin, like all drugs, will eventually engender resistance."

Malaria (see photo) has proved capable of evolving to escape whatever humans throw at it, whether through the immune system or through chemistry. With 5,300 genes, plasmodia are much more complex targets than a virus like HIV. What is more, their 12-step lifecycle includes a variety of distinct physical forms that grow in human liver and red blood cells as well as in mosquitoes. Fortunately, human bioscience is also evolving, and modern biotechnology brings to the battle highly sophisticated tools for picking apart the parasite and finding its weaknesses. The question is whether these tools can deliver affordable medicines accessible by the nearly three billion people inhabiting malaria-infested regions. Even more fortunately, some of the major biotech players are establishing novel cooperative partnerships, based on no-royalty intellectual property agreements that promise to alter the economics of future malaria treatments.



Red blood cell infection by the malaria parasite *P. falciparum*

One major instance is the cooperative agreement between the Medicines for Malaria Venture (MMV), headquartered in Geneva, and two American biotechnology research leaders based in Cambridge, Mass., Genzyme Corp. and the Broad Institute. These three bring together a combination of advanced genetic and drug screening techniques, high motivation and global contacts to speed drug development. Their goal is to establish an endless pipeline of malaria drugs — one new clinical candidate every five years — and stay ahead of the parasite's capacity for evolution.

Origin of the Partnership

In the beginning there was Professor Dyann Wirth, who chairs the Department of Immunology and Infectious Diseases at Harvard University's School of Public Health. Wirth's specialty is drug resistance in protozoan parasites such as the malaria-causing plasmodia. She employed genetic sequencing and gene modification to identify the cellular mechanisms inducing drug resistance. In 2002, other researchers reported that they had sequenced the entire *P. falciparum* genome. As a followup, Wirth and colleagues in 2006 published an analysis of the worldwide diversity in that genome. They paid special attention given to mutations associated with drug resistance.

The malaria genome diversity project took place at the newly founded Broad (rhymes with road) Institute, a collaboration between Harvard and the Massachusetts Institute of Technology (MIT). In the words of Roger Wiegand, associate director of Broad's Infectious Disease Initiative, one important purpose of the new institute is to “foster local collaborations within Boston's biotech community. Before, MIT, Harvard and all the companies were acting as independent players. There was no integration.”

Wirth was one of the Infectious Disease Initiative's co-directors. During the period when the malaria genome work was coming out, Henri Termeer, Genzyme's chairman and chief executive officer, was searching for ways in which he could harness his company's resources to find solutions for ignored diseases in the developing world. This goal in 2006 took the form of Genzyme's Humanitarian Assistance for Neglected Disease (HAND) program.

The Broad-Genzyme connection was a natural one. “We started talking in 2005,” recalls Genzyme Senior Vice President James Geraghty. “Dyann Wirth said her lab at Broad was doing breakthrough work. They were looking for an industrial partner to develop new drugs based on the targets genetic sequencing was identifying. As we talked, we realized we had the technology they needed.”

Genzyme had the ability to turn drug concepts into drug candidates, but it did not have the clinical expertise to test the candidates in humans. For that, the new partnership turned to the Medicines for Malaria Venture (MMV), which bills itself as “philanthropic venture capital.” It was founded in 1999 and specializes in public-private partnerships for drug development.

MMV, among other strategies, creates “miniportfolios” with pharmaceutical companies that involve developing antimalaria compounds from the earliest lab experiments. MMV developed a miniportfolio with Genzyme and Broad Institute that became the largest of three such arrangements. MMV also has partnerships with other research sites around the world. This network enables it to organize clinical trials to bring drugs to market. In return for MMV's drug development work, Genzyme and the other miniportfolio companies have granted the organization royalty-free licenses for distributing any approved drugs in malaria-endemic countries. Government and nonprofit malaria programs will receive these drugs at cost.

Fitting the Pieces Together

MMV's Wells observes, “The collaboration is a tribute to Jim Geraghty's and Dyann Wirth's vision. Always in a successful partnership, there have to be people at the top committed to changing global health. Then you need people below who are motivated to make it happen.” The talks between MMV, Genzyme and Broad mapped out a collaboration that takes advantage of each partner's special capabilities.

The Broad Institute, with its push-the-envelope technology, is central to the partnership. Broad researchers are actively examining variations in plasmodium and human genes associated with differences in disease severity. This research can yield new treatment

strategies, such as inhibitors for the plasmodium version of dihydroorotate dehydrogenase (DHODH), a critical cell enzyme.

Apart from target discovery, the Broad Institute's Infectious Disease Initiative also has a drug discovery component. The rise of drug screening assays that test hundreds of compounds simultaneously has greatly accelerated drug development. Broad uses two types of assays. One checks for malaria parasite killing capacity — it basically consists of red blood cells and parasites in an array of 384 small wells. Another assay tests for inhibition of specific molecular targets identified through genetic analysis. The first type of assay identified a lead family of potent compounds whose exact mechanism of action has yet to be defined. The second advanced lead compound arose through the second method, by testing inhibitors of plasmodium DHODH.

Aside from that antimalaria compounds that Broad has independently spotted, Genzyme brings a library of 300,000 compounds for the institute's scientists to test. "Plasmodium is not particularly protected against drugs. We find about four promising agents per thousand compounds screened," reports MMV's Wells.

Genzyme's more important contribution is after those compounds are detected. The company's scientists first work to optimize the compounds' structures. They also test for cell toxicity. This is a point at which many agents are rejected. They have to be selective malaria killers; they can't kill the human cells too. If they pass this hurdle, Genzyme then tests the compounds in animals. First come the tests for stability — a drug will not be much good if the body eliminates it rapidly. Next are tests for effectiveness in animal models of malaria. Genzyme hopes to be able to have a compound ready for early human testing in 2011.

MMV also brings money to the table. The organization spent \$54 million dollars in 2008 on malaria research, of which \$3.8 million went to the Genzyme/Broad miniportfolio. After Genzyme does its preclinical work and readies a drug candidate for human testing, MMV's clinical trial network will go into action. If the trials are successful, MMV will escort the drug through regulatory approval and find manufacturers and distributors for it. Genzyme and Broad may or may not be involved in this later phase. MMV usually grants the rights to the relatively small, private, for-profit market to a corporate partner when developing new drugs. The company in exchange pays part of the human trial costs. The Broad/Genzyme/MMV collaboration has not yet had to face this issue.

Organizational Hurdles

Jeffrey Klinger, Genzyme's vice president for the HAND project, says that he was skeptical when he first heard about the malaria project. "We're just a medium-sized company making a modest

investment. How could we make an impact?" asks Klinger. "We had to enable each group to accomplish things it couldn't get done by itself. We overcame personality and cultural issues to create a very efficient cross-disciplinary team."

One of the issues involved differences in organization. Genzyme followed an industrial team approach. Klinger notes that while there are 40 or 50 Genzyme staff involved in the malaria research, their total work is the equivalent of only nine or 10 full-time employees. People come and go, contributing their skills as required. The process builds a dynamic synergy. "This flow requires just the right amount and flavor of project management," says Klinger. "You have to be flexible, but still steer the ship. A colleague of mine, Carol Sherako, does exactly what a project manager is supposed to do."

Broad Institute follows a somewhat different model, bringing together a collection of individual lead researchers with labs at Harvard and MIT as well as its own in-house scientists. Roger Wiegand recalls that he "flipped the priorities a bit" when he joined Broad because his history was in drug development rather than basic science. Since he asserted his influence, "Broad has hired more drug development people, with an emphasis on things the pharmaceutical companies aren't doing" — one of these being malaria drug screening.

A major stumbling block at the beginning was the intellectual property rights issue. Although Genzyme had made clear at the beginning that it would assign rights to a nonprofit organization like MMV, the university lawyers were still interested in protecting their institutions' interests. "We had to keep telling people that there was no pot of gold at the end of the malaria rainbow," recalls Wiegand. Agreement was reached when Harvard and MIT agreed to follow Genzyme's lead. They too gave MMV royalty-free licenses allowing the organization to supervise drug development.

Wiegand concludes, "In the end we obtained a completely transparent exchange of information. You can't tell who is from where at the meetings." The collaboration's management team now meets on a daily basis with larger whole project meetings occurring biweekly.

As drugs start to advance, those meetings are expanding to include chemists, toxicologists and other specialists. The collaboration itself is expanding. To further identify and refine drug candidates, it has worked with contract research partners in India, as well as the International Centre for Genetic Engineering and Biotechnology laboratory in New Delhi. Chem Partners in Shanghai synthesizes many of the prototype compounds that have emerged. Exchanges with these entities take place weekly.

Overseeing this process is MMV's yearly review of its projects, conducted by the organization's advisory board. "We got grilled," Wiegand reported after the July 2009 annual conclave and before the board issued its findings. "They asked a lot of probing questions and wanted a few things tweaked. But mostly things seemed OK."

Enlightened Self-Interest

One question that stands out in this collaboration is why Genzyme, a biotech success story with \$5 billion in annual revenues, is interested in malaria. Klinger responds, "We couldn't do what we are doing without the new funding organizations, the advances in biomedical knowledge and the commercial sector's change in attitude. Before, the companies were not interested in malaria drugs because there was no money in it. Now many are showing enlightened self-interest."

Klinger argues that there is a real desire among pharmaceutical company personnel to make a positive contribution to neglected epidemics like malaria. "It is very attractive to people," he says. "When I tell people about this everyone wants to sign on." Challenging work using the most advanced scientific methods, along with having a personal impact on improving the world — who can resist?

But there is also the self-interest side to his company's efforts. All poor nations have a middle class able to buy advanced medications. In countries like China or India, that population is very large. Genzyme's Geraghty says, "Our goal is to be a partner and improve countries' health. We have our own products to market [in developing countries], although those products are very expensive and for a small group. We need to gain the cooperation of national governments, and malaria is very important to them."

A certain confluence of interests sparked Genzyme's involvement. The company is not alone in this. A number of larger, more established pharmaceutical companies are also working with MMV. These include GlaxoSmithKline, Novartis and sanofi-aventis. But, observes Wells, "Genzyme is a smaller organization, and the vision has permeated further there."

By David Gilden

Upending Malaria Economics

The private, for-profit market also buys malaria drugs, at a price substantially higher than the nonprofit sector pays. Novartis charges developing countries' public programs 80 cents for an adult course of Coartem[®], its artemisinin combination therapy. These countries' commercial wholesalers pay about \$4 per treatment. In the United States, the Coartem wholesale price is \$70.

Even with these price differentials, the private market has not proved large enough to support commercial development of new malaria drugs. Neither have U.S. and European orphan drug laws. These laws extend market exclusivity and provide tax credits for drugs that treat rare diseases, which in rich nations includes malaria. To open up the drug pipeline, the U.S. Congress in 2007 approved a windfall for developers of drugs to fight malaria and 15 other tropical diseases. Companies that see such drugs through to approval by the U.S. Food and Drug Administration (FDA) will receive a "priority review voucher" for some future drug. The voucher ensures accelerated review of a new drug, frequently leading to six months or more of extra time on the market. This difference could be worth several hundred million dollars in additional profits from a blockbuster drug.

The availability of this bonus is constrained by other U.S. laws regulating drug marketing rights. If the company owning the voucher does not have a new drug appropriate for the voucher, it can sell the voucher to a drug producer that does. Novartis was the first company to receive a priority review voucher when the FDA approved Coartem in April 2009. A Novartis executive told *The New York Times* that the voucher was "a gift from heaven."

Though its exact value is still a matter of speculation, the added income from the voucher promises to transform tropical medicine into a modestly profitable venture. That income can go to support more malaria drugs — or it can go to enrich corporate coffers.

MMV estimates that the vouchers are worth \$80 to \$150 million. It reckons that this sum is enough to pay for advanced human trials. When MMV trades private sector marketing rights to corporate partners in exchange for financial support of these trials, it now includes consideration of the vouchers. Its contracts divvy up their eventual value in relation to each partner's investment.

TB Alliance Partnership Charts Course for Future Neglected Disease Treatments



Lessons Learned:

- *All parties must have trust in each other and commitment to a common goal.*
- *With international partners, the project requires effective communications and regulatory strategies.*
- *Proactive market research can identify challenges that will inform product development and distribution.*



A TB patient is evaluated by a nurse at the Brooklyn Chest Hospital in Ysterplaat, Cape Town, South Africa.

Photo by Eric Miller

A global clinical development program, developed and managed by the Global Alliance for TB Drug Development (TB Alliance) and Bayer HealthCare, is evaluating the commonly prescribed antibiotic moxifloxacin for use in a new, first-line tuberculosis (TB) treatment. If successful, the clinical trial program will deliver what may be the first new TB drug approved in more than 40 years — one that saves lives because it will be part of an affordable, shorter TB regimen that is widely accessible and adoptable by economically disadvantaged countries and health care systems in the developing world.

Of no less importance, though, are the lessons learned in overcoming the challenges leading up to this historic partnership, as well as those encountered during this TB drug registration program, which is one of the first to be conducted according to modern regulatory standards. The TB Alliance and Bayer partnership, along with various supporting public and academic organization relationships, represents a potential win-win situation between a not-for-profit organization and a profit-oriented

pharmaceutical company that has an existing commercially available drug that has been successful in the global market.

The partnership is ahead of its time with innovative strategies that can benefit the field of TB drug development and accelerate the progress of new treatments for neglected diseases.

New Drug for TB Desperately Needed

Tuberculosis usually attacks the lungs but can also affect the central nervous, lymphatic, circulatory, genitourinary and gastrointestinal systems, as well as bones, joints and even skin. It is responsible for killing nearly 1.8 million people worldwide every year. The World Health Organization (WHO) estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis*, the organism that causes TB, resulting each year in nine million new cases of active TB. China and India alone account for 35 percent of all estimated new TB cases each year. An estimated one billion will be newly infected between 2000 and 2020; 200 million will fall ill and 35 million will die. Making the problem even worse, multi-drug-resistant tuberculosis (MDR-TB) is an emerging infectious disease threat classified as a category C priority pathogen by the National Institutes of Health.



A researcher at Tiervlei Trial Center in Bellville, Cape Town, South Africa, one of the facilities where the TB Alliance and its partners are evaluating moxifloxacin in tuberculosis patients.

Photo by Eric Miller

Today, therapy for drug-sensitive TB is based on a four-drug regimen to prevent the development of drug resistance. That regimen consists of isoniazid, rifampin, pyrazinamide and ethambutol. Discovered 40 or more years ago, each of these drugs must be administered for six to nine months, often under the direct observation of a health care provider. A shorter TB treatment could improve patient adherence to treatment, lower the rates of treatment failure and relapse, and ultimately reduce the emergence of drug-resistant strains that are more deadly, as well as more costly and burdensome to treat.

Developed and marketed since 1999 by Bayer HealthCare, a unit of Leverkusen, Germany-based Bayer, moxifloxacin has been shown in animal studies to be effective against the organism that causes TB. Preclinical studies commissioned by the TB Alliance in 2002-03 and conducted by investigators at The Johns Hopkins University have found, for example, that substituting moxifloxacin for isoniazid in a mouse model system decreased the amount of time needed to eradicate TB infection by two months.

A moxifloxacin-containing regimen has the potential to reduce TB treatment time from six or more months to four.

Finding Common Ground

It is uncommon for major drug companies to provide best-selling patented drugs for use against diseases of the poor. Many fear the loss of brand equity in serving poor countries due to possible gray market sales, overuse and misuse, and the possible loss of sales in their primary target markets — wealthy residents of North America, Europe and Japan.

With this challenge as a backdrop, the TB Alliance had to develop a flexible and adaptable strategy at the onset to make the case for moxifloxacin as an affordable TB treatment with a company like Bayer. How does a not-for-profit organization establish a win-win situation for a profit-oriented pharmaceutical company that has an existing commercially available drug that is successful in the global market?

“It seems pretty clear that to manage this and other challenges that arise throughout a project of this magnitude, you first must establish a foundation of trust, mutual respect and commitment to the project for all the parties involved,” says Dr. Mel Spigelman, president and chief executive officer of the TB Alliance, a not-for-profit, product development partnership. “In early negotiations it was integral for each organization to take time to understand the needs and potential reservations of the other as well as to the end user; this process takes time and may be incremental. Today, our organizations work well together and listen to each other because the knowledge, judgment and expertise of each organization were clearly communicated in the negotiating process.”

The TB Alliance and Bayer agreement to develop moxifloxacin for TB brings together some of the world’s leading institutions that already had some knowledge of the drugs’ potential and had an interest in doing independent research. These institutions include the U.S. Centers for Disease Control and Prevention’s TB Trials Consortium, The Johns Hopkins University Center for Tuberculosis Research, the Centre of Medical Microbiology of the Royal Free & University College Medical School at University College London, and the British Medical Research Council Clinical Trials Unit.

Under this historical agreement, the collaborative effort is clearly defined:

- Bayer provides drug development know-how, supplies moxifloxacin (and matching placebo) and will serve as the regulatory sponsor for any U.S. and global registrations.
- University College London serves as the sponsor for the Phase III TB trial, called REMoxTB, and is the home institution of this trial’s chief investigator who provides therapeutic area clinical and laboratory expertise.

- The British Medical Research Council provides clinical trial expertise, particularly as it relates to studies conducted in Africa, and develops and manages the REMoxTB trial database.
- The TB Alliance serves as the lead coordinator of the moxifloxacin clinical development program and hires and oversees contract research organizations to carry out a number of key functions, including packaging, stability testing, releasing and distributing good manufacturing practice-compliant study drug and ensuring good clinical practice-compliance at study sites through site monitoring and auditing. It also ensures compatibility of the clinical and safety databases of the different trials, and coordinates final combined data analysis and writing of the integrated clinical study report. The TB Alliance is also addressing the issue of global clinical trial capacity by the TB Alliance clinical trial site assessment project. Sites selected to participate in the REMoxTB study receive training from the TB Alliance and its partners in conducting registration standard TB drug trials.
- Centers for Disease Control and Prevention's TB Trials Consortium sponsored two global Phase II trials that evaluated moxifloxacin in nearly 800 combined subjects.
- The Johns Hopkins University Center performed much of the research throughout the development of moxifloxacin, including acting as sponsor for a Phase II trial conducted in Brazil.

“The success of this project depends on a combination of experienced, knowledgeable veterans who obviously know what they are doing and can think out of the box,” says Spigelman. “This leads to trust and confidence, which are the key underlying elements whether there is a profit or not.”

Public-Private Partnership Breaking New Ground

It was important for both organizations to mutually commit to the goals of the partnership, as well as to acknowledge and respect concerns specific to each organization's business model. Once an understanding was cemented, the parties quickly aligned under an agreement that established the most significant clinical development program for the treatment of active TB since the late 1960s.

“This clinical trial program is unique in its dimension for TB development,” says Dr. Martin Springsklee, vice president of global medical affairs for Bayer HealthCare. “It is the first of its kind in TB — to evaluate an existing compound for a new use for neglected disease and gain regulatory approval.”

With partners and sites on five continents, the members of the partnership recognized the project requires effective, communication-based industry and regulatory standards, an especially daunting challenge given the different languages and cultures represented across the vast geographical scope of the clinical trial sites. The partners tackled this issue by forming an array of working groups, operational as well as strategic oversight committees, and developing a local network of contacts that identify and reach key decision-makers and appropriate individuals in each location.

Few clinical trial sites have the capacity and experience to conduct large-scale pivotal registration trials of TB drug candidates, a long standing roadblock to TB drug development. To help remedy this situation for the future and identify potential sites suitable for moxifloxacin pivotal registration trials, the TB Alliance initiated a clinical trial site assessment project to evaluate potential sites. Presently, 93 sites have been assessed, and a number of these sites have been selected for participation in the ongoing Phase III REMoxTB trial. These assessments are available publicly, via a database, and are an important contribution to the scientific and clinical infrastructure needed to support current and future clinical TB research.

As no drugs for TB have been registered according to modern regulatory standards, little regulatory guidance exists to facilitate the approval of new TB regimens by global regulatory and standard-setting authorities. Working together with industry and advocacy partners, the TB Alliance initiated a dialogue with the U.S. Food and Drug Administration, European Medicines Agency,



Pill burden often poses an obstacle to a patient's ability to complete treatment.

Photo by Atul Loke



A tuberculosis patient at the Brooklyn Chest Hospital in Woodstock, Cape Town, South Africa, is given a dose of the standard four-drug TB regimen, which he must take regularly for six months under the observation of medical staff.

Photo by Eric Miller

the WHO and a number of high burden countries, through its Open Forum series, to address key issues in the critical path to TB drug registration. Bilateral discussions specific to moxifloxacin are also under way with regulatory agencies.

“The standards that will stem from these activities will be influential because there are no completed registration programs for TB drugs in the modern regulatory environment,” says Dr. Ann Ginsberg, head of clinical development at the TB Alliance. “We’re charting new territory; it’s a learning curve for everyone because the moxifloxacin study is designed to simultaneously establish pivotal data while building capacity.”

In preparing for the launch of a moxifloxacin-containing regimen, initial market access research identified that universal adoption will be a much more difficult and protracted process than originally envisioned due to a lack of established global- and country-level processes for adopting and implementing new TB regimens. To solve this problem, the TB Alliance initiated a “Country Introduction Study” to understand the issues a country might face when adopting, introducing and making available a new TB regimen, once a new TB drug is recommended by global technical agencies. The results will help establish a regulatory strategy for moxifloxacin registration and identify countries that might be engaged to actively introduce a moxifloxacin-based TB treatment regimen.

The TB Alliance and Bayer also have developed an adaptable forecast model to estimate future demand for moxifloxacin for TB treatment and prepare for manufacturing if the drug is registered and adopted for first-line therapy of TB.

“This program is much broader than just about developing moxifloxacin as a potential TB treatment,” says Bayer’s Springsklee. “It will also pave the way for building clinical trial capacity and expertise in TB endemic countries.”

Progress Being Made

Moxifloxacin is in clinical trials to evaluate its potential for treatment-shortening for TB. The Bayer-TB Alliance clinical development program includes three completed Phase II trials and an ongoing pivotal REMoxTB trial. Upon completion, these trials will have enrolled more than 3,000 TB patients. These completed Phase II trials were at sites in Africa, Europe and the Americas, including 10 in the United States. Two drug regimens are being evaluated: the first substitutes moxifloxacin for ethambutol, and the second substitutes moxifloxacin for isoniazid in the standard four-drug treatment regimen. REMoxTB will determine whether these new, four-month regimens are not inferior to standard six-month therapy in terms of failure and relapse, as well as safety.

REMoxTB patient enrollment began in January 2008. A total of 20 to 30 sites, including ones in Asia, Africa and Latin America, are being recruited into the study to reach enrollment targets. Assembling this network of sites has spurred an assessment of the readiness and capabilities of TB clinical trial sites worldwide; a total of 195 sites contacted, and 93 sites in 42 countries have been assessed as of August 2009. Thirty-four REMoxTB protocol-specific assessments have been conducted in addition to these baseline assessments in 19 countries. Assessments related to

capacity to support MDR-TB trials have also been conducted in eight countries as part of the overall site assessment project.

Public health experts await the registration of a shorter moxifloxacin-based TB regimen and the subsequent expansion of the underlying knowledge base, capacities and standards necessary to accelerate clinical testing, registration and introduction of additional new regimens. Ultimately, a new regimen will lessen the burden of TB for patients and health systems alike and save lives.

“It is interesting. When you shed past dogmas and look objectively at what we’ve collectively been doing for almost the past decade, it makes all the sense in the world,” says Spigelman of the TB Alliance. “Doing something novel takes time for people to accept.”

By David Perilstein

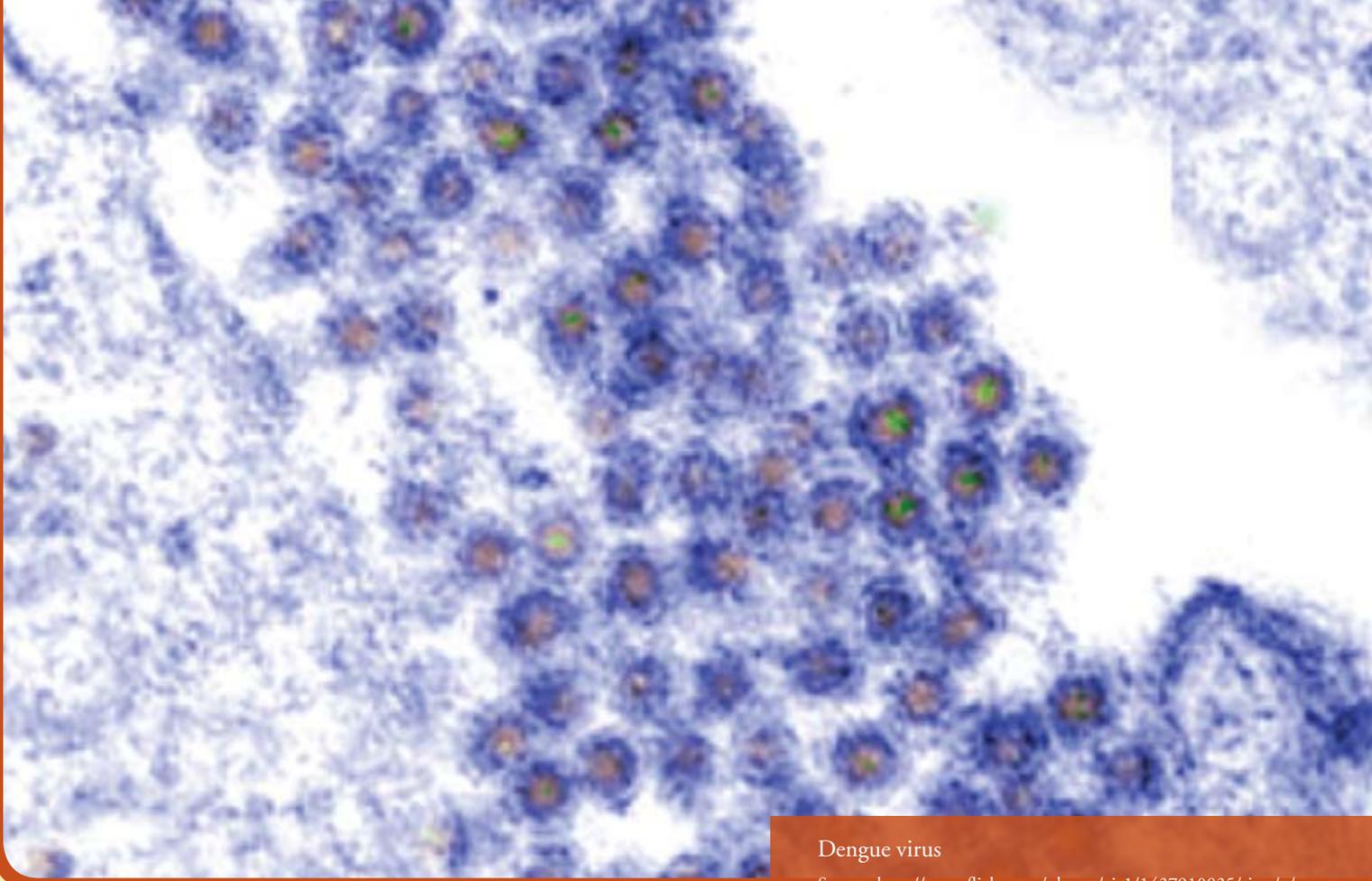


Dengue Fever Partnership Changes the Rules for Vaccine Development



Lessons Learned:

- *Moving critical processes, such as research, development and distribution, into resource-poor countries with high disease burden can help alleviate the slow trickle down of treatment discoveries from richer countries.*
- *Breaking a large initiative down into individual tasks helps plan proper time and resource allocations.*
- *Having key partners with strengths in regulatory negotiation or other crucial areas ensures the right people are working on the right things and keeps a project moving forward.*



Dengue virus

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Dengue fever is an increasing problem worldwide. The dengue fever virus is spread by the *Aedes aegypti* mosquito, which is highly adapted to urban conditions. A vaccine will be key to controlling the disease. The Pediatric Dengue Vaccine Initiative (PDVI) partnered with Brazil's state-owned Instituto Butantan to rapidly develop a promising vaccine candidate. Butantan, which supplies Brazil with most of its vaccines, is also receiving advice from PDVI contractee Global Solution for Infectious Diseases. The trio aim to develop the vaccine in the next few years and bring it to market at a low price. After approval, PDVI will continue to assist with planning for mass distribution. The development route taken by this vaccine represents a new model. Previously, large pharmaceutical companies introduced vaccines in rich countries first. It took years for the vaccine to appear in resource-poor countries. With the dengue fever vaccine, both research and distribution will take place in a developing country with a strong interest in moving quickly against the disease.

The Dengue Fever Epidemic

Dengue fever is on the upswing in most tropical areas of the world, particularly south Asia and Latin America. The epidemic spread of the disease has made dengue vaccine research a pressing matter. Donald Francis, vaccine pioneer and executive director of Global Solutions for Infectious Diseases (GSID), thinks that the novel international collaboration behind dengue vaccine development represents a new paradigm. "There is a major evolution going on," he says. "Vaccine development is moving from the industrial world and its enormous investments to the developing world where the diseases occur. The NIH [U.S. National Institutes of Health] used to license vaccines to rich country companies and then years later the vaccines would get to developing countries. Now the NIH is going directly to the developing countries. Both for-profit and nonprofit government entities are playing a role. They used to be "me too" operations making established vaccines. These groups are getting more interested in development."

Isaías Raw (pronounced "rao") is director of the Instituto Butantan as well as president of its research branch, the Fundação Butantan. Butantan is owned by the state of São Paulo, where dengue fever is "out of control," says Raw. "Every summer [January through

A Global, Urban Epidemic

Dengue, sometimes referred to as “breakbone fever,” notoriously involves severe flu-like symptoms, an extensive, hypersensitive rash and excruciating joint and muscle pain. There are currently about 36 million symptomatic cases per year worldwide. Asymptomatic cases amount to three times that figure. Conversely about six percent of the clinical dengue fever cases — 2.1 million — contract life-threatening dengue hemorrhagic syndrome. Supportive treatment greatly reduces mortality, which amounts to about 20,000 yearly. Children are especially affected by dengue fever’s severe consequences.

Even the asymptomatic cases are important because they help spread dengue via the disease’s mosquito vectors, mainly *Aedes aegypti*. “You can’t really control the mosquito,” says Brazilian vaccine pioneer Isaías Raw. “It lives in very small bodies of stagnant water. In cities, it lives in so many vases, tanks and potholes. It’s very difficult now with the huge urban migration that we’ve seen. Mosquito control was done many years ago, but today it is not a good solution. We used to dust every place with DDT. It’s a stable compound, but it destroys birds and bees and hurts the forest. Today, we need a vaccine.”

March] is worse than the last.” Brazil as a whole recorded 560,000 cases in 2007, with 158 deaths. In the first 35 weeks of 2008 — the latest period for which data are available — there were already 735,000 cases and 212 deaths. Aside from São Paulo state, Rio de Janeiro state and parts of the north are heavily affected.

Brazilian-International Partnership

Profiting from the NIH’s recent tilt toward developing-country vaccine producers, Instituto Butantan has obtained a license to a promising dengue fever vaccine from the agency. Efforts to create HIV or malaria vaccines involve northern agencies and companies collaborating to develop the candidate vaccines and then work with developing country researchers to conduct human testing. The location of vaccine manufacture has not yet come up in these cases but will most likely include developing-country producers that receive no-royalty licenses. The dengue fever vaccine collaboration gives the local partner much more authority. It yields project direction to Brazil’s Instituto Butantan as soon as the vaccine comes out of the NIH laboratories. This public Brazilian agency is the

country’s main vaccine manufacturer. It will organize the human trials for the dengue vaccine, steer it through regulatory approval and bring it to market.

This is the first time that Butantan has attempted to develop a new vaccine from early human safety trials on. To provide technical support for this ambitious effort, Butantan called on the Pediatric Dengue Vaccine Initiative. PDVI is based in Seoul, South Korea. It is a branch of the International Vaccine Institute, which was established in 1987 under the aegis of the United Nations Development Programme.

According to Richard Mahoney, PDVI’s director, vaccine access, “We started in 2003, and became a coalescing force.” PDVI, among other things, organized regular meetings to bring experts together. These meetings provided a venue for real sharing of information and setting of standards. The Bill & Melinda Gates Foundation in 2003 granted PDVI \$55 million to support its activities, including establishing vaccine trial sites in Asia and South America. PDVI thus became a leader in creating the global dengue vaccine effort along with such agencies as the World Health Organization.

Butantan, with PDVI’s assistance, hopes to implement an ambitious plan for rapidly moving from safety studies to large-scale efficacy trials and mass rollout. PDVI has, in turn, brought in GSID as management and training consultants. “GSID has experience in scaling up vaccine trials. It sits down with Butantan and talks about technical requirements and then comes back and does an audit,” says Harold Margolis, PDVI’s director.

Butantan is able to move a vaccine from the development stage to distribution. Mahoney has great respect for its capabilities. He comments, “Brazil has made dengue a high priority, and we have made Butantan a high priority among developing country manufacturers for developing the vaccine.” Butantan is a government-owned, nonprofit entity but works like a private company. It is able to pump its revenue back into its facilities so as to maintain an efficient, high-quality operation.

PDVI Facilitates Vaccine Development

Developing a dengue vaccine should be a straightforward affair, but there are two serious obstacles. Dengue virus has four strains, designated dengue 1-4. The people at highest risk of life-threatening dengue hemorrhagic syndrome are those who were previously infected with one strain and are later infected by another. The solution to this problem is to create a vaccine that triggers long-term high antibody levels to each strain. Butantan’s NIH-licensed vaccine generally showed signs of provoking strong

immunity in preliminary U.S. trials. Francis praises the NIH approach. He says, “Rather than the old-fashioned live-virus culture approach to create attenuated strains here they directly manipulate the genes and then clone the virus. It’s incredible.”

There is, however, a further issue. The immune response to each strain in the combined vaccine interferes somewhat with the response to the other strains. Multiple dosing promises to provide long-term immunity despite this interference. The optimum vaccine dose and schedule has to be worked out in carefully designed human trials. Here, PDVI has played a critical role in advising on appropriate trial design and the required lab capabilities.

PDVI has also worked with Butantan to assess potential trial sites, in the process evaluating local epidemiological information and research infrastructure. The initiative also did an elaborate computer analysis of the entire vaccine project, breaking it down into more than 320 individual tasks, including trials, building manufacturing capacity and regulatory approval. These analyses allow Butantan to navigate new territory for their institution, indicating the resources and time that would have to be allocated.

PDVI has been instrumental in clarifying the vaccine’s regulatory pathway with government officials at Brazil’s National Health Surveillance Agency — the equivalent of the U.S. Food and Drug Administration. Mahoney says, “One of the most important things we do is to bring detailed technical knowledge to discussions with the regulatory agency. We then help Butantan provide scientifically accurate and relevant information in its applications for clinical trials and, eventually, for marketing approval.”

Raw adds, “PDVI has a first-rate team of experts to analyze the results and plan the next step. Having PDVI shows outside recognition and gives the project more credibility.” That credibility is vital when seeking support from the state or from private funders.

After Approval

Vaccine approval is, of course, only one step on the way to vaccine access. Vaccines in the past have been introduced first in rich countries and then very slowly made their way to developing ones. This process could take years. Recent vaccines, such as those for pneumococcal bacteria and human papillomavirus, have come to market at unprecedentedly high prices, making their use in resource-limited settings still more problematic. But there will not be much need for the dengue fever vaccine in areas able to support high prices. The vaccine will go straight to poor countries with small health budgets and poor distribution systems.



Aedes aegypti mosquito

Yet there is no doubt that the vaccine will be highly advantageous in these nations: A 2004 Southeast Asia cost-effectiveness study found that a 95 percent effective dengue vaccine with a public sector price of 50 cents would be very cost effective. It is not clear if a price of 50 cents per dose can be achieved but PDVI’s free support work will help reach that target. Then too, the Instituto Butantan is state-owned. Part of its mission is to keep prices down. When explaining PDVI’s strategy, Mahoney says, “Butantan will be a low-cost manufacturer that just covers its costs. One of the little secrets of the vaccine business is that the major cost is in R&D, whereas production costs are low. Sometimes the cost of packaging is more than cost of making the vaccine.” PDVI is working with Butantan on an analysis of actual costs to establish a rational basis for the vaccine’s price.

Mahoney has long experience in reducing vaccine expense. As secretary of the International Task Force on Hepatitis B Immunization, he was one of the key personalities in bringing down developing nation prices for the hepatitis B vaccine. In 1986 the worldwide price for this vaccine was about \$100 for the required three doses, and the U.S. private sector cost is still nearly \$70 for children (more than \$150 for adults). It is now available in resource-restricted settings for less than 90 cents for three doses, or under 30 cents per dose. (The older childhood vaccines typically cost less than 10 cents in less developed countries versus a U.S. public sector price of \$10 to \$20 per dose.)

Butantan intends to sell its dengue vaccine in other Latin American countries once it has obtained regulatory approval and has sufficient manufacturing capacity. Making the vaccine is just the first step toward mass immunization, which necessitates a multi-phase introduction effort. Health care workers require training on the appropriate population and schedule for the vaccine. Health

organizations need to conduct a community education effort to ensure public interest. Supply chain logistics have to be worked out in detail — is there enough cold storage space, for example?

Contemplating the post-approval phase of dengue vaccine development, Margolis says, “Nearly everyone in low- and middle-income countries receives vaccines through public programs. PDVI will work to get in place funding mechanisms through GAVI [Global Alliance for Vaccines and Immunization] and local country governments. We also will advise on technical implementation and help to conduct demonstration projects.”

A New Paradigm in Vaccine Development

PDVI is moving forward on several other fronts. In India, it is advising vaccine makers on developing the NIH vaccine. In Thailand, PDVI's epidemiologic studies have helped French vaccine developer Sanofi Pasteur with its large-scale dengue vaccine efficacy trial. The Sanofi Pasteur dengue vaccine is the first to reach this advanced testing stage. If all goes well, the world will see several competing dengue vaccines by the middle of the next decade. The promise of multiple sourcing leaves PDVI hopeful. Mahoney and

Margolis contend that competition among producers is a potent means of keeping prices down while keeping supply up.

In January 2009, the Instituto Butantan announced an agreement to develop a leishmaniasis vaccine with the Seattle-based Infectious Disease Research Institute. Although the vaccine will target the leishmania reservoir in dogs, the agreement in many respects parallels the Butantan-PDVI agreement for dengue fever. In both cases, Butantan, with the assistance of an international nonprofit partner, will adopt a vaccine concept and develop it into a marketed product.

Butantan is growing into an autonomous vaccine developer that can produce vaccines for diseases of local concern. It will be able to license vaccines for such diseases as malaria, tuberculosis and HIV when the National Institute of Allergy and Infectious Diseases and other research organizations find promising candidates. Butantan will then be in a position to ensure that these vaccines become accessible to the public in Brazil and other developing countries.

By David Gilden

Global Access License Between University and Biotech Benefits Developed and Developing World



Lessons Learned:

- *There is no standardized approach to drafting or enforcing global access language in licensing agreements.*
- *Having an industry partner that is like-minded in its sense of global stewardship is an essential foundation for a successful agreement allowing a company to advance technology for the developed world.*
- *Support from senior leadership at the stakeholders' organizations is important given the unique nature of global access provisions.*



Kishor M. Wasan, Ph.D.

Photo by Martin Dee, with permission of UBC Public Affairs.

An oral amphotericin B (AmpB) formulation is showing promising results in preclinical studies that could one day provide the developing world with a treatment for leishmaniasis, a devastating disease that has a significant impact on indigent populations where the disease is endemic. An oral AmpB formulation would allow the therapy to be brought to the patient instead of requiring travel to the clinic, and it does not appear to have the associated renal toxicity of available intravenous (IV) formulations, putting an affordable, less toxic therapy within reach of the developing world for the treatment of leishmaniasis.

The success to date is due in no small part to global access principles that bind researchers, university staff and students, and the licensee of the technology in a common bond — to ensure this novel, lipid-based oral formulation of AmpB reaches the developing world where, according to World Health Organization (WHO) statistics, leishmaniasis currently threatens 350 million people in 88 countries. The licensing deal, the first among Canadian

universities in accordance with these global access principles, was signed in 2008 between iCo Therapeutics Inc. and the University of British Columbia (UBC), both of Vancouver, British Columbia, Canada. In return for the worldwide exclusive rights to develop and sell the oral reformulation of AmpB (termed iCo-009 by iCo Therapeutics) in the developed world as a treatment for blood-borne fungal infections, iCo Therapeutics ensures the availability and accessibility of a suitable formulation for the developing world to treat leishmaniasis.

Leishmaniasis: A Global Threat

Leishmaniasis, a parasitic disease transmitted by the bite of the sand fly, infects an estimated 12 million people today, and about two million infections occur annually. It has a wide range of clinical symptoms:

- Cutaneous leishmaniasis, the most common form of the disease, causes ulcers on the face, arms and legs. While the ulcers heal on their own, they cause serious disability and leave severe and permanent disfiguring scars that lead to discrimination, stigma and substandard living conditions. Epidemics are especially devastating in refugee camps.

- Visceral leishmaniasis, the most severe form of the disease, attacks the internal organs, and, if left untreated, is fatal within two years.

An ominous global trend is developing, where persons with HIV become coinfecting with visceral leishmaniasis, which accelerates the onset of AIDS by cumulative immunosuppression and by stimulating replication of the virus.

According to the WHO, visceral leishmaniasis is no longer restricted to endemic areas and the number of cases of visceral leishmaniasis and HIV coinfection will continue to rise. For example, up to 70 percent of adult cases of visceral leishmaniasis in southern Europe are linked to HIV infections, and 35 percent of all leishmaniasis patients in some areas of Ethiopia are coinfecting with HIV, with an indication that it is spreading to neighboring countries such as Sudan.

Where There's a Will, There's a Global Access License

The promising oral AmpB formulation was discovered in the Wasan Lab at UBC by Kishor M. Wasan, Ph.D., professor, Canadian Institutes for Health Research/iCo Therapeutics research chair in drug delivery for neglected global diseases, and chair in the Division of Pharmaceutics and Biopharmaceutics, and Ellen Wasan, Ph.D., adjunct professor in the faculty of pharmaceutical sciences also at UBC. The Wasans devised an oral formulation that showed promising lab results with minimal side effects, a significant improvement on the 50-year-old treatment that is expensive, must be administered by IV infusion and is highly toxic. The significance of this innovation grew when they realized it was ideal for application in both the developed and developing world.

The next step for moving the Wasans' discovery from the lab bench through to commercialization might have followed the traditional route charted by most technology transfer offices that patent and license university-based innovations. However, in 2007 UBC's University-Industry Liaison Office (UILO) had just become the first university in Canada to develop a flexible framework to ensure it provides global access to relevant technologies. The new Global Access Principles, developed in collaboration with key senior administrators and the student-led UBC Chapter of the Universities Allied for Essential Medicines, establishes practical mechanisms and partnering strategies for UBC technologies to maximize their societal impact.

So when iCo Therapeutics, a publicly traded biotech company, approached the UILO about the Wasans' discovery, they needed to find a win-win solution that would achieve both organizations' objectives.

"Our goal was to have the new oral AmpB formulation licensed to a company that would agree and be able to not only develop the formulation in the developed world for fungal infections, but also develop the technology in the developing world for the treatment of leishmaniasis in accordance with the Global Access Principles adopted by UBC," says Ian Bell, a technology transfer manager of the UBC UILO, which assists UBC researchers through core activities of sponsored research and technology transfer to increase the academic, societal, environmental, economic and financial impacts of their research.

John G. Clement, Ph.D., chief business officer and director of iCo Therapeutics, adds, "Our business model is focused on redosing or reformulating drugs with clinical history for new or expanded indications. The oral amphotericin B program is an early proof of concept of the underlying drug delivery technology and provides iCo with an opportunity to expand our product pipeline and provides a new way for the company to explore other drugs that can be converted from the parenteral route of administration to the oral route."

The licensing negotiations — described as very productive and positive by those involved — occurred over roughly a four-month time frame and involved various parties, including UILO, the UILO external legal counsel, iCo Therapeutics and its external legal counsel.

The most critical negotiation issues involved the licensing terms related to:

- Reasonable development time lines — With the need to move both a developed and developing world formulation forward, the partners established a development time line to ensure that the company could pursue a product for the developed world that could financially support the company, while at the same time, ensuring that the product for the undeveloped world would not be pushed aside or pursued in favor of the other.
- Formulation for developing world — The partners agreed to a process whereby iCo would either solve any issues in its obligations to create a developing world formulation, or UILO would have the ability to step back in and access the rights to develop the formulation for the developing world.
- Parallel imports — In an attempt to prevent or reduce the risk of parallel imports, a matter of great concern to iCo Therapeutics, the partners agreed that different formulations would be developed for the developed and developing worlds. The nature of the formulation actually lent itself to this strategy because of the different requirements, such as disease target, and temperature and stability.

Once these issues and the financial terms were agreed upon, much of the discussion centered on the appropriate global access language, since the desire to increase global access for health-related innovations and the realities of working with industry to commercialize them takes more than a standard licensing structure.

“UBC granted iCo Therapeutics the worldwide, exclusive license to the UBC technology,” says Bell. “Under the license agreement, iCo’s global access obligation is to ensure availability of a formulation of the UBC technology for treating leishmaniasis in the developing world at a subsidized price.”

Public and Private Partners

In May 2008, the UBC UILO signed its first licensing agreement in accordance with Global Access Principles when it partnered with iCo Therapeutics to advance the oral formulation of AmpB. As the Wasans’ discovery moved from the lab bench through to licensing, it also involved several public and private organizations:

- Federal government of Canada — Provided research funding to the inventors through the Canadian Institutes for Health Research and the National Research Council of Canada Industrial Research Assistance Program (NRC-IRAP), designed to provide funding and support to Canadian small- and medium-sized enterprises. iCo Therapeutics also received NRC-IRAP funding to support development activities related to the oral formulation.
- Canadian Research Network and Mathematics of Information Technology and Complex Systems — Provided funding for a UBC postdoctoral intern to work with iCo Therapeutics to develop the technology further.

Since signing the license agreement in 2008, iCo Therapeutics has moved development of the formulation forward. Some of the work includes collaboration with the Consortium for Parasitic Drug Development — a Bill & Melinda Gates Foundation-funded consortia based at the University of North Carolina at Chapel Hill — to test the oral formulation in a leishmania model. The results of this testing showed that the oral formulation was almost 99 percent effective in clearing the infection. iCo Therapeutics also held a pre-IND (investigation new drug) meeting with the U.S. Food and Drug Administration to clarify the company’s clinical plan.

iCo Therapeutics also is in the planning stages of chemistry, manufacturing and controls, scale-up and current good manufacturing practice, and good laboratory practice safety and toxicology work to support a IND application.

Flexibility, Support and Willingness Key to Success

The UBC UILO has had some experience over the years with global access and individual licensing programs and projects. One program involves a UBC-based researcher who collects marine and plant biota, such as sea sponges from Papua New Guinea, and then isolates potential therapeutic compounds from them, with a portion of economic returns going back to the country of origin. The UBC UILO also manages some projects with the aim of developing essential medicines for the developing world that received a Grand Challenges in Global Health grant from the Foundation for National Institutes of Health and the Gates Foundation.

But now, with adoption of Global Access Principles and the licensing agreement to allow iCo Therapeutics to commercialize the oral formulation of the drug AmpB, UBC is part of a growing number of universities and nonprofit research institutes that have either implemented or are considering adopting socially responsible licensing practices.

“Looking back over the hard work and discussions that culminated in this licensing agreement, I think three key elements stand out — flexibility, support and a willingness to do something good for those who are less fortunate,” says Bell at the UBC UILO. “And, in a way, it was the result of a perfect storm and a little luck.”

Key learnings that came out of this licensing agreement include:

- **Flexible Language:** This win-win scenario was based on mutual trust and iCo Therapeutics being receptive to a creative and flexible approach used by the UBC UILO in developing the licensing terms and language that were acceptable to all parties. There is not a standardized approach to drafting or enforcing global access policy language in licensing agreements.
- **Support:** The UBC UILO was pleased by the support it received for the Global Access Principles by external stakeholders during the review process. iCo Therapeutics welcomed the global access language in the license and its investors agreed the global access language and relationship with UBC were a benefit to all.
- **Willingness to Do Good:** Having an industry partner with a global stewardship priority is the foundation for a successful agreement allowing a company to advance technology for the developed world, while making the technology available to resource-constrained countries through subsidized pricing.

Support from senior administration, both at the university administration and technology transfer office, also is critical to the adoption and implementation of global access principles that guide how licensed university-based technology may impact the developing world. This support allowed for the drafting of appropriate global access licensing terms and is helping to establish a new metric to measure the effectiveness and global influence of UBC and the UILO.

“We are very excited by the potential of iCo-009,” says iCo Therapeutics’ Clement. “We are proud to know that iCo-009 could save and improve the quality of life in both the developed and developing worlds.”

By David Perilstein

University of British Columbia Global Access Principles

To maximize the societal impact of University of British Columbia technologies, practical mechanisms and partnering strategies are required that:

- Enhance both the economic and societal impact of university innovations
- Extend these impacts to broader global settings
- Ensure fair access to these technologies for the world’s poor within an evolving framework of licensing practices, legal concerns, business opportunity and time constraints

Broadening the societal impact of and global access to UBC technologies requires that these concerns are addressed when new UBC technologies are developed, patented and licensed. To this end, while applying the university’s intellectual property policy, UBC will:

- Promote global access by entering public-private partnerships to develop new technologies to benefit the developing world
- Prioritize environmentally friendly research and green alternatives and take the lead in community sustainability
- Respect biodiversity, ensuring value return to countries of origin
- Endeavour to ensure that underprivileged populations have at-cost access to UBC research innovations through negotiated global access terms whenever appropriate

As the understanding of issues relating to societal licensing evolves, balancing ambitious objectives with legitimate business concerns requires patience, determination and the willingness to be both pragmatic and flexible. To support this social licensing commitment, UBC will, where possible, employ the following strategies:

- Build on the values of access and dissemination as demonstrated in the open source movement in the information technology sector.
- Promote the use of nonexclusive licensing of research tools (for example, the West Coast Licensing Partnership on Flintbox™).
- Consider field-of-use and jurisdictional limitations in exclusive licenses to exclude developing world countries.
- Negotiate developing world access at-cost to relevant technologies that are licensed on a worldwide exclusive basis (required for technology development).
- Continue to seek partnerships with not-for-profit and charitable organizations to provide much-needed funding for neglected disease area.
- Design patent strategies with development partners that ensure quality product delivery to those most in need, while promoting sustainable, local infrastructure.

In measuring the success of technology transfer activities at UBC, societal impact has become a key metric alongside standard throughput, financial and economic measurements. Positive societal impacts include improving human and veterinary health, supporting international biodiversity, protection of the environment and promoting sustainable green alternatives.

New Broad-Spectrum Vaccine Protects Against Most Pneumococcal Disease



Lessons Learned:

- *Building a committee that emphasizes the collaborative nature of the development work provides focused expertise when implementing complex projects.*
- *Frequent, timely communication is a critical aspect of a successful partnership's information sharing.*
- *A for-profit product can be developed alongside a nonprofit product when similar goals exist.*
- *People in resource-rich countries often benefit from technological advancements designed to aid people in developing countries.*



Courtesy of the PneumoADIP, photo by Adrian Brooks

Pneumococcal disease kills approximately 1.6 million people every year, with more than half of these deaths occurring to children less than five years old. The variances in strains are compounding the problem. “Pneumococcal disease has over 90 serotypes,” says John Boslego, M.D., director of PATH’s vaccine development global program. “It is the most common cause of severe pneumonia, which is the leading killer of children less than five years of age worldwide.” The pneumococcus bacterium also causes meningitis, sepsis (blood infection) and otitis media (inner ear infection).

Current pneumococcal conjugate vaccines approved for use in children are effective against strains common in the industrialized world and some developing countries, but they do not cover all pneumococcal serotypes, including several strains common in Africa and Asia. They are also expensive, which makes access to vaccines difficult in poorer countries that most desperately need them. While the GAVI Alliance is helping low-income countries

afford the current vaccines, new vaccines are needed both to improve protection and affordability. Other licensed pneumococcal polysaccharide vaccines cover an estimated 23 serotypes but are only effective and approved for use in adults. A pneumococcal vaccine that is affordable and offers broad serotype independent protection for use in children in the developing world is urgently needed.

Conjugate vaccines are complex, difficult to produce and expensive for the populations most in need of protection from pneumococcal disease. Since conjugated vaccines do not work against every type of the disease or for everyone who needs protection, protein-based vaccines could be a promising, affordable alternative that could offer broad protection to populations that need them worldwide, especially children in developing countries.

“The development of a common protein vaccine against the disease holds particular promise because it could provide broad protection by covering all pneumococcus serotypes, saving the lives of millions of children around the globe,” says Boslego.

To advance such a vaccine, PATH — a U.S.-based nonprofit organization whose mission is to create sustainable, culturally relevant solutions that enable communities worldwide to break longstanding cycles of poor health — and the Austrian biotechnology firm, Intercell AG, are partnering on a recombinant protein-based pneumococcal vaccine. The partnership aligns the goals of each organization: Intercell's pursuit of a vaccine for the elderly in the industrialized world and PATH's goal of an affordable vaccine for infants and children in the developing world. The common interest is to develop a pneumococcal vaccine with broad protection across the many serotypes of pneumococcal disease. While there may be differences in the vaccine formulations for children or the elderly, they will likely share the same antigens. By building on this synergy, the partners are striving to achieve both global public health and commercial goals.

Should the common protein approach prove effective, it would offer universal coverage across all pneumococcal serotypes and prevent serotype replacement that can occur with conjugate vaccines. In addition, the manufacturing technology for protein vaccines is more simple and cost-effective relative to conjugate vaccines and could, therefore, lead to a vaccine that would be affordable for distribution by public health systems in low-resource countries. Finally, if successful, the vaccine could have a significant commercial value in the developed world where pneumonia is a major cause of morbidity and mortality in the elderly, the immune-suppressed and post-operative populations.

The Path to Discovering a Single Broad-Spectrum Vaccine

Assuming a standard recombinant protein manufacturing process, it is less cumbersome and less expensive to produce protein vaccines than complex multivalent conjugate vaccines. Intercell's IC47 pneumococcal vaccine consists of three proteins that are highly conserved in all 90-plus different serotypes of *S. pneumoniae* including a selected panel of pneumococcal strains from different geographic regions. "Thus the vaccine could be able to protect against all disease-causing pneumococcal strains and isolates," says Dr. Andreas L. Meinke, head of Alliance and Grant Management at Intercell AG.

Intercell AG has developed the IC47 pneumococcal vaccine based on its proprietary Antigen Identification Program®. One of the three antigens, PsaA, was licensed by Intercell AG from the U.S. Centers for Disease Control and Prevention (CDC), and all preclinical work, including the toxicity study and all manufacturing of the three recombinant proteins was performed by or on behalf of Intercell AG.

PATH and Intercell AG are working together through a collaborative research and development agreement that covers all stages of development through Phase II clinical studies, including draft guidelines for the terms of a commercialization agreement between the parties to be negotiated prior to the start of Phase III clinical studies. However, the development work is funded in stages and based on successful achievement of established milestones.

In the case of the collaboration with Intercell, PATH did a comprehensive landscape analysis starting in 2005 with a focus on protein vaccine candidates. Intercell had one that was attractive to PATH so Intercell submitted a proposal and PATH agreed to move forward with it. Because PATH believes the success of any collaboration depends on the selection of a good partner, PATH conducted a thorough assessment, in accordance with its own standard operating procedure, before entering into a formal collaboration with Intercell. During this process, PATH routinely:

- Assesses the reputation of the company, its corporate behavior and its economic viability to ensure compatibility with PATH's mission and reputation;
- Reviews the scientific and technical capabilities of the collaborator to make sure they are appropriate for the collaboration; and
- Ensures that the public health outcomes and return on public-sector investment will be commensurate with the effort involved in establishing and maintaining the collaboration.

In the end, PATH and Intercell decided that a partnership would be mutually beneficial to both entities and entered into a vaccine development agreement in 2006. In general, PATH's agreements with partners including Intercell, cover, at minimum, the following information:

- The objectives of the collaboration, the roles and responsibilities of each partner, and the expected outcomes;
- The accountability and performance milestones that will be used to ensure that the goals of the collaboration are met;
- A clearly defined management and decision-making structure of the collaboration; and
- A clearly stated process for monitoring, evaluating and terminating the collaboration.

PATH began collaborating with Intercell during the preclinical development of the IC47 protein-based vaccine candidate in 2006 and has since committed an additional \$3.6 million to support clinical development through the second quarter of 2010. In addition to developing the vaccine candidate, Intercell AG has also agreed to make the vaccine affordable for children in developing countries as part of a global access commitment under this project. The development of the vaccine for the elderly will be carried out in parallel using Intercell's own funding.

Trials and Lessons Learned

In March 2009, Intercell AG launched a Phase I first-in-man trial of IC47 in healthy adults in Germany with support from PATH. PATH and Intercell bring complementary expertise to the project. They also share development costs. Funding from PATH has covered approximately one-half of preclinical development expenses, thus reducing Intercell's risk. Without this funding, Intercell would likely have emphasized developing a vaccine for elderly people in Europe and the United States rather than expanding the target market to also include children in low-income countries. Successful preclinical development from 2006 through 2008 paved the way for the Phase I clinical trial in healthy adults beginning earlier in 2009.

In partnership, Intercell and PATH have been able to further advance the IC47 vaccine candidate by utilizing tools such as genome sequencing data developed and made publicly available through the work of PATH and other partners, as well as by bringing together other collaborators in preclinical evaluation.

This project is the first at Intercell AG to be fully developed from preclinical research to clinical testing. The trial also marks an important milestone for PATH's pneumococcal vaccine project in advancing the development of a protein vaccine candidate through preclinical studies into clinical trials.

The main two antigens were identified via Intercell's Antigen Identification Program, and tested together with the third antigen from CDC in various animal models of pneumococcal disease as recombinant proteins, produced by Intercell. The manufacturing of the recombinant proteins for the Phase I clinical trial was done by a contract manufacturing organization under close collaboration with Intercell. Thus many tasks during the preclinical research as well as development phases needed exploratory work, expert advice and support by third parties.

Further clinical studies are currently in the planning and preparation phase. The sites remain undetermined at this point, but the goal is to move as quickly as possible to the target population of children and infants in the developing world. Although it is beyond the scope of the current agreement, the eventual goal of the collaboration is to conduct a Phase III efficacy trial in infants in developing countries. Intercell is also planning a separate trial in elderly adults in developed countries.

"Our collaboration with Intercell has facilitated the advancement of a promising pneumococcal common protein vaccine candidate through preclinical studies into clinical trials," says Mark Alderson, Ph.D., director of PATH's pneumococcal vaccine project.

One factor that makes this project unique is the pursuit of an innovative scientific approach for which there is no proof of concept or a previously charted regulatory pathway. As a result, the partners have to exercise extraordinary care in designing the Phase I and II studies and build in clear go/no-go decision points. "Go/no-go" decision points in the PATH/Intercell collaboration are contingent upon whether the goals of both entities can be met and are still in alignment, as well as establishing consensus on major project components such as the design of clinical trials and outcomes to measure, among others.

To make the vaccine low-cost for the developing world, the partners are working to improve production efficiency, purification processes and stability. They invested early in assessing these issues to mitigate risks and build back-up options in case the need arose.

"It is certainly easier than the development of a conjugated vaccine, but there are also challenges to be addressed," says Andreas L. Meinke, Ph.D., of Intercell. "Similar as for conjugated vaccines, the three recombinant proteins have to be formulated in a common buffer with the selected adjuvant without compromising the immunogenicity and efficacy of any of the components. In preclinical studies this goal was achieved and, thus, we proceeded to clinical testing."



Courtesy of the PneumoADIP; photo by Adrian Brooks

“In addition, assays to evaluate efficacy in clinical studies have to be established for protein vaccines,” adds Meinke. “The assays which have been developed for conjugated vaccines are not readily applicable to protein vaccines. A further challenge to the development of protein vaccines is the fact that conjugated vaccines are already licensed and need to be used as comparator. Thus protein vaccines will likely need to be superior to already licensed conjugated vaccines.” A definition of superiority could include performance and broader serotype coverage, but could also constitute more cost-effective and simpler manufacturing that enables global access to the vaccine.

Discussions to reach agreement on the terms of the collaboration between PATH and Intercell took approximately one year from first introductions and scientific discussions to completion of the agreement and initiation of the project. PATH and Intercell are using an iterative partnership approach for project management.

All facets of the project — including problem-solving and decision-making — are managed collaboratively through a vaccine development committee that meets regularly in person or via teleconferences.

Each organization brings expertise and resources to the partnership. While Intercell’s core expertise was originally in discovery and preclinical development, the company has already begun building expertise in late-stage product development. PATH provides expertise in nonclinical development, manufacturing, clinical development and, particularly working in developing countries, which is where the Phase II and III trials will be performed. The partners are sharing the development costs for the first phase. PATH’s contribution reduces the risk Intercell might incur by investing in a vaccine for uncertain markets in poor countries.

By Pam Baker

A Glaucoma Treatment Option With Global Promise



Lessons Learned:

- *License terms between academic and for-profit entities can be crafted to address global access for important medical technologies in a meaningful way.*
- *Developed countries should assist the global health effort by funding the advancement of treatments exclusively targeted at those in resource-constrained settings.*
- *Companies can successfully commercialize products in the large markets of the developed world to help support a sustainable solution for those in resource-constrained countries.*
- *A company's ability to use tiered pricing may be a valuable incentive.*



Photo by Shutterstock® Images

Ophthalmologists in the developed world use a variety of available options today to treat glaucoma, including pharmaceutical eye drops, laser procedures and surgery. In the United States, where almost three million have glaucoma, eye drops are the first choice for decreasing eye pressure and eventual blindness, followed by a combination of medications and laser treatment that safely controls eye pressure for years.

However, in developing countries, where people have the highest risk of developing blindness from glaucoma, varied treatment options are almost nonexistent, leaving trabeculectomy — a complex procedure requiring a significant amount of surgical skill and follow-up care — as the therapeutic intervention of choice, according to a *British Journal of Ophthalmology* article “Glaucoma in West Africa: a neglected problem.” The reasons for limited options in the developing world: availability of modern treatments that are generally expensive compared to patients’ income, the need to travel long distance for care, and possible lifelong treatment and unpleasant side effects. The author, Peter R. Egbert, M.D., professor emeritus, Department of Ophthalmology at Stanford University School of Medicine, wrote, “We desperately need a more effective means of treating glaucoma... A simple, rapid, inexpensive

and effective surgical procedure would be of great benefit. What we need is a procedure for glaucoma that is as reliable and cost-effective as modern cataract and intraocular surgery.”

A promising response to this plea involves glaucoma drainage devices (GDDs), some of which are on the market, while others are being developed by large biomedical device companies and promise to offer reasonable safety and effectiveness for the control of intraocular eye pressure. One patented GDD is the Aquashunt™, a Yale University invention licensed with humanitarian terms to a leading ophthalmology business, OPKO Health Inc., which started conducting human clinical trials in South America in 2009.

If successful, inventor M. Bruce Shields, M.D., the Marvin L. Sears professor and chairman emeritus of the Department of Ophthalmology and Visual Science at Yale University School of Medicine, and the Yale University Office of Cooperative Research, both of New Haven, Conn., as well as the Miami-based OPKO Health, expect the new GDD to provide hope not only to the 60 million people afflicted with glaucoma in the United States and other developed nations, but especially to those in developing parts of the world where glaucoma is a leading cause of blindness and for which there exists no practical treatment.

Glaucoma — A Group of Diseases That Steals Sight Without Warning

Glaucoma is a large group of eye diseases that gradually steal sight without warning. The common feature is a progressive disorder of the optic nerve that causes a loss of peripheral vision and “cupping” of the optic disc. Experts estimate that half of the people affected by glaucoma may not know they have it because they are asymptomatic, especially in the early stages of the disease when peripheral vision loss is subtle and easily compensated for. While the medical understanding of the nature of glaucoma has changed in the past few years, it is a major public health concern globally. There is little known about primary prevention of glaucoma; however, there are effective methods of medical and surgical treatment if the disease is diagnosed in its early stage. Through appropriate treatment, sight may be maintained; otherwise the progression of the condition leads eventually to severe restriction of the visual field and irreversible blindness.

According to the Glaucoma Foundation and the World Health Organization, glaucoma is the leading cause of bilateral irreversible blindness worldwide and affects an estimated 60 million people, of which more than 20 million have been positively diagnosed and are being treated. Estimates predict this number to exceed 60 million globally by 2010, with more than 8.4 million people bilaterally blind from the disease.

Shaping a Humanitarian Solution for a Major Unmet Medical Need

Despite advances in ophthalmic surgery, especially in the fields of cataract, cornea and retinal surgery, many glaucoma specialists recognize they need a better solution than surgery to control intraocular pressure in patients with glaucoma. The traditional surgical approach drains the eye fluid (aqueous humor) to a superficial part of the eye called the conjunctival space, but this can lead to scarring and failure, in some cases, and leakage and infection in others.

Shields of Yale, whose research has led to more than 200 scientific papers and book chapters, with a special focus on the mechanisms and management of glaucoma, has invented a novel GDD medical device called the Aquashunt as a treatment for glaucoma. Composed of a biocompatible material that conforms to the shape of the eye, the Aquashunt is designed as a rapid, simple and minimally traumatic implant, making it ideal for use in both the developed and developing world. It drains aqueous humor from the anterior chamber to the suprachoroidal space — a space that exists between the sclera and choroid layers of the eye.

“A lot of people are looking for better operations,” says Shields. “But I was looking for a simple and fast glaucoma procedure that would offer a high success and low complication rate that, once

completed, patients in the developing world wouldn’t have to make frequent trips for checkups.”

In 2006, Aquashunt was awarded its first U.S. patent. With the help of Yale’s Office of Cooperative Research (OCR), a startup company, Vidus Ocular, was created to further the concept for the developing world.

“If not for Yale’s Office of Cooperative Research, this project would have gone no further,” says Shields. “Three OCR licensing professionals got the patent approved, and then they worked with me to find venture capital and a business team.”

The Management Team and Investment Comes Together

John Puziss, Ph.D., director of technology licensing at Yale’s Office of Cooperative Research, says the path that led the licensing professionals to a management team and investment started with a single conversation.

“In marketing the technology to the venture capital community, one of our members, Loraine Lombard, pitched it to Myles Greenberg of Collinson, Howe and Lennox, an early-stage health care venture capital firm,” Puziss says. “Greenberg suggested talking to ATV Capital, which, in turn, recommended Nick Warner as an experienced engineer who would be a good addition to the management team. Nick subsequently led us to Jim McNab, who led us to Ben Bronstein.”

Vidus Ocular started with the one issued patent, licensed from Yale’s OCR, three patent applications, and about \$1.3 million in funding provided by the company’s founders and individual investors, including Jim McNab, a self-described serial investor and entrepreneur.

“Dr. Shields is not a serial inventor but a clinical glaucoma researcher. He is someone who has spent his life working on a simple, well-thought-out application that is less complicated than others being developed,” McNab says. “I got involved because I knew we were going to have an edge on the competition.”

As a company co-founder and investor, McNab worked with Shields and the OCR to help build a structure for the startup company with the addition two other co-founders, physician Ben R. Bronstein, and engineer Nicholas F. Warner, both of whom could help Shields get a second generation device approved for use. (While working with GMP Companies Inc. of Fort Lauderdale, Fla., Shields had developed a first generation version of the Aquashunt, which had successfully undergone preclinical trials in pigs prior to the license reverting back to Yale’s OCR in 2005.)

“We were able to get enough early-stage funding to build a prototype, test Dr. Shields’s design and conduct successful in vitro and in vivo studies in rats,” says McNab. “We had a compelling story and good data, but we had a central issue: How much money would we need to build an infrastructure and marketing department to get to the next phase. We needed to attract more funding.”

McNab started talking with venture capital groups throughout the United States, but negotiations and terms were more than the entrepreneurial company felt it could afford.

“Our goal was to quickly get this device into the marketplace so it could be used all over the world,” McNab says. “We felt we had a good shot at this.”

Unsuccessful with the venture capital route and unable to spark any interest with foundations, McNab turned to ophthalmic companies where he got “lucky” when he reached out to OPKO Health’s Chairman and CEO Phillip Frost.

“Frost and his OPKO team recognized that the market is large enough that it could successfully commercialize Aquashunt in the developed world and not have to make a lot of money in the developing world, which was the desire of Dr. Shields and a condition of the OCR humanitarian-based license,” McNab says. “They recognized it is the right thing to do because the Aquashunt device is a simple, powerful idea that will have utility all over the world. A year or two from now, I think this will be borne out.”

Yale Implements Humanitarian License Provision

On May 7, 2008, OPKO Health announced it had acquired Vidus Ocular and retained Shields as a consultant, Bronstein as executive vice president of R&D, and Warner as senior director, product development. Under the terms of the agreement, OPKO also agreed to work with Yale University on a number of initiatives to increase access to the Aquashunt technology in the developing world.

As part of Yale’s intellectual property management, the OCR includes humanitarian provisions in licenses that allow for a return on investment in more profitable markets.

“Yale’s objective in helping to fund Vidus Ocular was to create a new venture that would focus significant resources on the development of this important new treatment for glaucoma,” says Puziss at Yale’s OCR. “In addition, the university wanted to find a licensee that would commit to making Aquashunt readily accessible to patients in the developing world.”

Humanitarian Terms of a License

John Puziss, Ph.D., director of technology licensing at Yale’s Office of Cooperative Research, says Yale and OPKO Health Inc. settled on key humanitarian terms in the licensing agreement for Aquashunt:

- Licensee shall make the use of licensed products in low-income and lower-middle-income countries a part of its Corporate Mission Statement.
- Licensee agrees to use commercially reasonable efforts to pursue clinical testing of the licensed products in low-income and lower-middle-income countries.
- Licensee agrees that, upon achieving \$5,000,000 in cumulative profits (determined in accordance with [Generally Accepted Accounting Principles] GAAP) from sales of licensed products, Licensee will commit an amount equal to 1 percent of net sales, up to a maximum of \$500,000 per year, in the form of licensed products, grants and/or services, to governments in underdeveloped regions, or not-for-profit charitable organizations.

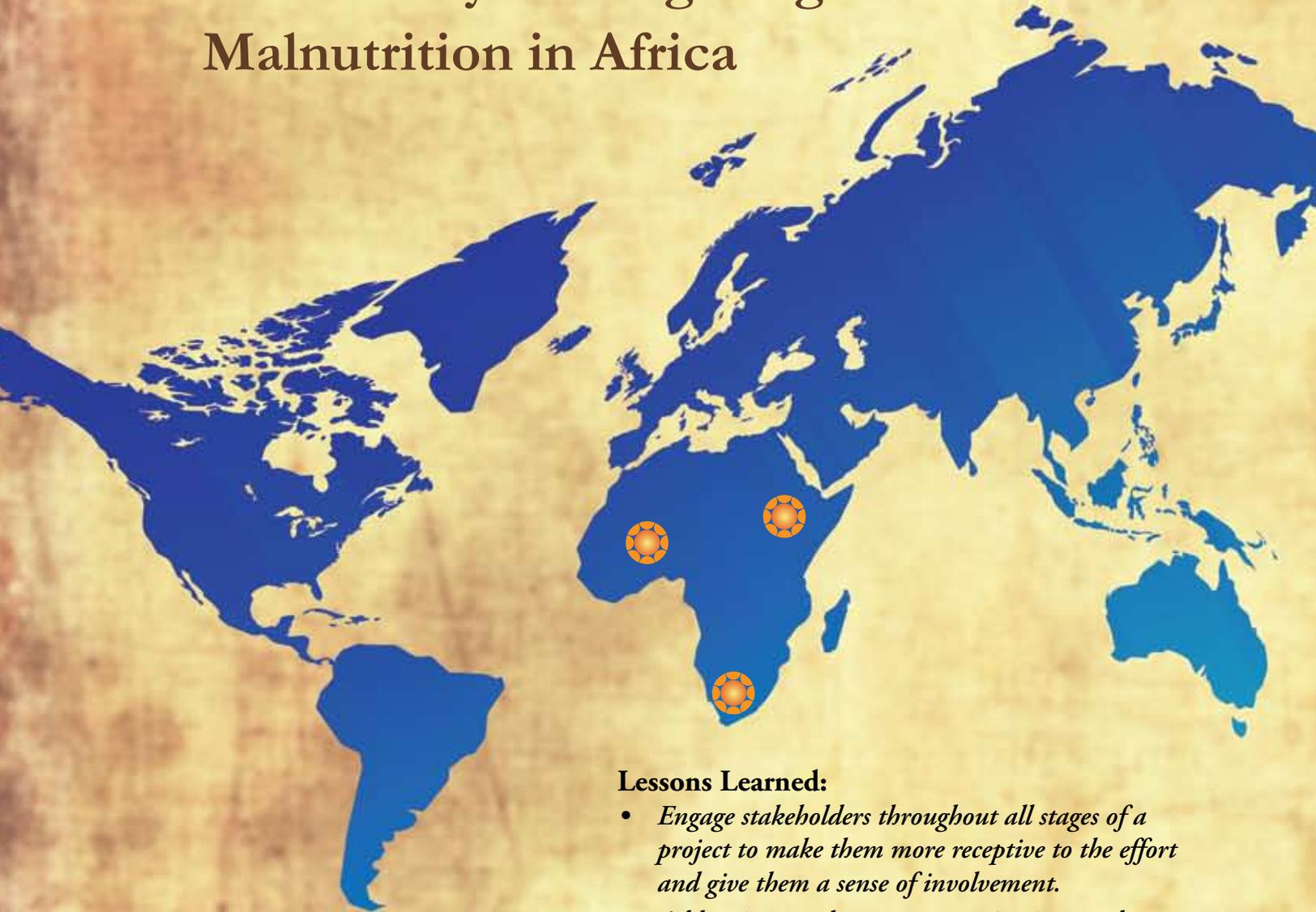
This sentiment was reinforced by OPKO’s Head of R&D Jamie Freedman, M.D., Ph.D.: “We believe the Aquashunt device is an innovative approach to the treatment of glaucoma and has significant potential to provide clinical benefit for patients who do not have easy access to medical therapy or for those who do fail medical therapy.”

OPKO Health started human clinical trials with Aquashunt in 20 patients with refractory chronic forms of open angle glaucoma, in the Dominican Republic in February 2009, followed by Mexico in July. Once data are collected from the clinical trials and six-month followup, OPKO plans to seek a CE mark for the device in Europe conduct a clinical trial for marketing purposes in Europe, and initiate a larger clinical trial in the United States to eventually obtain regulatory approval for marketing from the U.S. Food and Drug Administration.

“Even though my personal goal was to create a device that would benefit people in desperate situations in developing countries, this device should offer the same advantages to all, whether they live in developing or developed nations,” Shields says. “The continued development and validation of the new Aquashunt for glaucoma is our top priority in our quest to eliminate the blindness of glaucoma worldwide.”

By David Perilstein

The Africa Biofortified Sorghum Project Consortium: Food Safety and Fighting Malnutrition in Africa



Lessons Learned:

- *Engage stakeholders throughout all stages of a project to make them more receptive to the effort and give them a sense of involvement.*
- *Addressing regulatory communications and policy concerns early is critical for long-term success of the initiative.*
- *Effective internal and external communication is key. Visible, tangible results and word-of-mouth communication are the most effective method to promote a project that has potential to impact a large population.*



African Biofortified Sorghum Project Coordinator and Africa Harvest CEO Dr. Florence Wambugu speaks to a sorghum farmer about some of the challenges growers face.

More than half a billion people around the world rely on sorghum as a dietary staple. The genus of numerous species of grass, sorghum is a unique crop in that it grows in hot, dry environments. Its tolerance for drought and heat make sorghum an important food crop in Africa, where irrigation is not accessible or affordable.

Sorghum is indigenous to the African states of Ethiopia and Sudan, and several African states are centers of sorghum diversity. Widely consumed through a wet cooking process similar to porridge or baked as bread, sorghum lacks essential nutrients, such as vitamins, iron, zinc and lysine and is not easily digested. To address the otherwise-promising crop's inadequacies, an African-initiated and led consortium was established to develop a nutritionally improved sorghum that would contribute to food security and help fight malnutrition in Africa.

The Africa Biofortified Sorghum (ABS) Project Consortium is led by Africa Harvest Biotech Foundation International (Africa Harvest), an African-based international nonprofit with a vision of an Africa without hunger, poverty or malnutrition. Its mission is to use science and technology — especially biotechnology — to help the poor in Africa achieve food security, economic well-being and sustainable rural development.

“The majority of African populations cannot afford vitamins, micronutrient supplement tablets or fortified foods,” said ABS Project Coordinator Dr. Florence Wambugu. “In areas prone to malnutrition, food choices and the delivery of vitamins and micronutrients through a locally produced staple food, such as sorghum, would have significant impact on malnutrition. ABS has the potential to improve the health conditions for populations with limited food choices, who eat sorghum as their main food source.”

Africa Harvest, realizing that no single African organization has the infrastructure or capacity to successfully undertake the scientific endeavor required for a project such as this, formed a strategic alliance of private, public and academic organizations. Funding for the ABS consortium comes from the Bill & Melinda Gates Foundation.

Team Work

The ABS consortium required expert partners in areas of technology development, product development and management, as well as organizations that could create an environment in Africa that enabled the development and use of ABS. A *project steering committee* manages task-oriented committees, as well as special teams that provide support in areas such as public relations, regulatory affairs and intellectual property rights. An *external advisory board* made up of experts from key disciplines — primarily genetic engineering, health and nutrition, general agriculture, and development management — makes recommendations to the project steering committee, reviews project progress and gives strategic advice through reports and interactive meetings.

The ABS Project Manager and Director of Technical Programs for Africa Harvest Dr. James Micah Onsando reports to the steering committee and is responsible for implementing the committee's decisions. He handles administrative, sociopolitical and management issues within the consortium and leads the Team Leaders Management Group, which is comprised of team leaders from each of the consortium members who meet to discuss and agree on project implementation and strategy, set milestones, discuss results and data, and share information.

The Technology Development group includes Pioneer Hi-Bred International (Pioneer), which donated the initial technology; the Council for Scientific and Industrial Research (CSIR), which assisted in customizing and enhancing the technology for use in Africa, and the University of California, Berkeley, which has since left the partnership, but early on, studied sorghum digestibility and the various processing methods. Studies of agronomic trait stability, such as food preparation and milling qualities of transgenic ABS are conducted by University of Pretoria in South Africa and have been promising.

“The ABS project aims to place more nutritious seeds into the hands of the people who need it the most — the poor — who reside in remote areas and do not have access to fortified, processed food,” says Lloyd Le Page, Africa Harvest board member and biotech affairs and regulatory manager for Africa at Pioneer. “The project is truly African: a native African crop, developed by African scientists for Africans. We are seeing real progress and are confident that we can reach our goals.”

To date, the Technology Development team has successfully developed sorghum with target levels of traits in iron, zinc, lysine and improved digestibility. The ABS#2, as this transgenic event is referred to, has been field tested in the United States four times, in various locations and seasons. CSIR and Pioneer are still working on vitamin A traits.

Pioneer has successfully backcrossed the relevant traits of four major African sorghum varieties, Macia, Malisor 84-7, Tegemeo and Sima. Backcrossing breeds a hybrid with its parent or a similar plant in order to produce desired traits in a plant with characteristics of the original species. The team has also developed an efficient sorghum transformation system, a contribution to the international scientific community, which can be used to further enhance sorghum by adding other desirable properties, such as weed and pest control.

An essential goal of the technology team is to build African scientific capacity through the training of African scientists. To date, Pioneer has hosted six African scientists in its labs in Johnston, Iowa. Five of these scientists have returned to Africa and have begun leading development work in areas of technology transfer, capacity building and the success of the project's delivery and impact in Africa.

A second team of consortium members focuses on product development in Africa. The Product Development group is comprised of the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT); Africa Harvest and National Agricultural Research Stations (NARs), which are represented by the Kenya Agricultural Research Institute; Environmental and Agricultural Research Institute; and Agriculture Research Council.

ICRISAT focuses on selecting target sorghum germplasm, gene information that is common in wide geographic regions of Africa, conducting environmental biosafety studies and collecting sorghum varieties for gene-bank storage. NARs focus on confined greenhouse and field studies for agronomic trait expression and stability, selecting varieties of sorghum for breeding and training others in open-pollinated and hybrid sorghum work. The biosafety research of NARs is supervised by biosafety and regulatory experts from Africa Harvest. Finally, international consultants from Pioneer and ICRISAT supervise breeding work.

The third team is made up of Africa Agricultural Technology Foundation, CORAF/WECARD in West Africa and Africa Harvest. These regional agricultural research organizations influence national policies and are important to harmonizing

policies across country borders. This team is focused on intellectual property brokerage, audit and management, and works to ensure the global access strategy for charitable objectives is maintained throughout the project's development and deployment. Project advocacy for stakeholder awareness and support in Western Africa is managed by CORAF/WECARD, whose vision is to contribute to sustainable reduction of poverty and food insecurity in west and central Africa through agricultural-led economic growth and improving the agricultural research system of the subregion. Africa Harvest is focused on the project's technical and financial management, biosafety regulations, and overall project leadership and coordination.

In the project's formative stages, partners established a clear communications vision to create an enabling environment for all partners to implement the project successfully in a timely manner. A close-knit group of communication professionals from Africa Harvest, Pioneer and CSIR provide direction for the project and guide internal and external communications to ensure consortium members speak in one voice. Consortium members are engaged to leverage their own Web sites, newsletters and other outreach strategies to promote the initiative within their organizations as well as to outsiders.

Growing ABS

The ABS project has the potential to improve the nutrition of 300 million Africans who use sorghum as a staple or supplement food. Whereas many genetically modified crop projects go years without conducting a single field trial, the ABS project has conducted several field trials in the United States during its four-year existence. Project developers attribute this progress to the project's strong public acceptance and communication component, which helped create an enabling environment for the project. These trials show promising success and results that will support further studies in Africa to target product development and delivery.

The ABS project is still in its technology development phase, which will end after five years, in June 2010. At that time the project is expected to achieve proof of concept and be rolled into the new



Drs. Andile Grootboom and Luke Mehlo, both from South Africa Council for Scientific and Industrial Research, spend time in a Pioneer lab in Johnston, Iowa.

agriculture program. There may be an interim phase after this deadline to ensure effective transition into the agricultural program. The technological efficiency of ABS is being enhanced, so levels of target plant traits and expressions will evolve into the final product as the project progresses and will be carried into the second phase of ABS: product development and deployment.

The ABS consortium has found it challenging to keep all coalition members informed, engaged and on message. While budget limitations make it difficult for communication professionals from partner organizations to dedicate time and resources to the project, project leaders and scientists have come to appreciate the role of communication, and this issue is resolving.

Communication was especially difficult when ABS sought to establish field trials in Burkina Faso. While most of the consortium members are from Anglophone countries, Burkina Faso is a Francophone country, and a language barrier had to be tackled. Additionally, cross-cultural administrative challenges arose because of the differing work cultures of French- and English-speaking members. These challenges have been overcome through training, reciprocal visits, innovative communication methods, interpreters and commitments from both sides to learn one another's language.

When cultural issues arose in Burkina Faso, the initiative experienced political challenges when it applied for permits to conduct contained greenhouse experiments. After an initial attempt to secure permissions from the Genetically Modified Organisms

Executive Council, a South African regulatory body, failed, the ABS project established a political action committee and engaged the media to educate the public and policy-makers about the importance of biotechnology in dealing with the country's famine.

From these experiences, the ABS consortium took away many lessons, including the importance of engaging key stakeholders such as regulators and government officials prior to seeking permit or policy approval. In the same regard, the consortium found that scientific training of regulators is especially vital in Africa because regulators are appointed based on the political issues needing attention in their regions. It is crucial that regulators make decisions based on science, rather than political motivation.

The partners also realized that engaging public and private stakeholders, primarily scientists and sorghum farmers, throughout all stages of a project makes them more receptive to the project and gives them a sense of involvement. For farmers and government officials, visible, tangible results and word-of-mouth communication are the most effective method to promote a project such as ABS.

The Promise of ABS for Africa

ABS has been a landmark project in Africa because it is the only one of the Grand Challenges in Global Health projects with an African grantee organization (Africa Harvest) and African leadership to steer the initiative's vision and strategy. Among the benefits of this African lead is that more than 80 percent of the project budget has been spent in Africa to develop African scientific capacity, infrastructure, technology transfer and to ensure the creation of an enabling environment for future project deployment. The project has successfully pioneered the concept of a consortium of partnership among public and private, as well as representatives from northern and southern Africa, for strategic research and development to impact major challenges in Africa.

ABS has demonstrated professional and efficient project management of an 11-member worldwide consortium — a virtual institution in a sense. The success of the consortium can be attributed to the right people working at the right capacity in the right positions as well as consistent yet innovative approaches to teleconferences at every level of the partnership, regular planning meetings and effective internal communication.

By Ashley Mastandrea



Dr. Florence Wambugu explains to journalists about the different varieties of sorghum.

Lesotho Apparel Industry Unites to Fight AIDS



Lessons Learned:

- *In areas of high HIV prevalence, factory-based HIV interventions promise remarkable efficiency. Such programs can combine treatment and prevention service for a concentrated population.*
- *Educating and empowering workers helps to slowly change the attitudes of the larger community outside the factory, where workplace programs have less direct impact.*
- *Companies that buy products from factories in resource-constrained and HIV-burdened countries advance the global health effort by funding the workplace prevention and treatment programs, in turn, ensuring continuous supply of products. Cutthroat factory competition makes it nearly impossible for factories to fund such programs themselves.*



ALABA factory, Nien Hsing Garments

Lesotho is facing an HIV crisis equal in extent to neighboring South Africa's but lacks the resources of its larger neighbor. One bright spot is the surging apparel industry, which exports most of its production to the United States thanks partly to Lesotho's duty-free status. The nation has built a reputation for ethical labor practices, and this greatly enhances its appeal. The industry employs about 45,000 mostly female employees. A major threat to its stability is the 43 percent HIV prevalence among these women.

The Apparel Lesotho Alliance to Fight AIDS (ALABA) is a special factory-based intervention that provides workers with HIV testing, treatment and prevention services. It has received support from international organizations working to alleviate poverty and the mainly U.S. retailers that purchase Lesotho's products. The program now includes almost all the garment factories in Lesotho. ALABA faces the challenges of a conservative moral atmosphere, the female workers' poverty and disempowerment, and the stigma of HIV. These factors have led to difficulties in reducing HIV risk, low HIV testing rates and late initiation of treatment. ALABA is

making progress in these areas through its peer-educator program and workplace medical clinics.

Getting Industry Involved in Health Care

Lesotho is an independent mountainous nation completely surrounded by South Africa. The two million Basotho living there are in the midst of an AIDS epidemic as calamitous as any seen in the region. But Lesotho's small, homogeneous nature fosters creative solutions to the epidemic. ALABA is one such innovation that focuses on Lesotho's main industry. The group's name, which is also the Basotho's word for "to care for the sick," symbolizes both its local roots and international connections. It has united the country's garment factories and workforce, the largely U.S. brands that buy from these factories, and an international organization promoting southern Africa's economic development. These entities work together to provide workplace-based HIV treatment and prevention services.

Basotho garment workers represent a highly concentrated at-risk or already HIV-infected population. They are a cohesive social group with broad connections to the entire community. At the



A peer-education session takes place during lunch time at Precious Garments.

same time, the factory owners have become increasingly concerned about the devastating impact HIV is having on the stability of their workforce. Moreover, the U.S. brands see that funding ALAFA's work supports their reputation for corporate social responsibility.

There is no question that the HIV situation in Lesotho is dire. The United Nations estimates that about 22 percent of the adult population — or 270,000 people — is infected. The epidemic has pushed the average life expectancy down to 40 years. Without HIV, it would be around 66 years according to a U.S. Census Bureau projection. The reason for this dramatic cut in life expectancy is easy to find: Only about a quarter of Basotho needing antiretroviral therapy (ART) actually received it in 2007. Still that percentage has increased from the low single digits only three years earlier. HIV testing itself is rare: About 12 percent of Basotho knew their HIV status at the end of 2007. Again this figure represents a large increase over 2004. Even as HIV testing and treatment become more accessible, HIV fears and stigma remain a barrier to taking action.

When ALAFA conducted an anonymous HIV serosurvey among apparel workers in 2007, it found that 43 percent of those taking the test were HIV-positive. This is not a surprising result given that the majority of these factory hands are young women living in a high-prevalence urban environment. (Their male counterparts tend to migrate to South Africa for the mining jobs.)

On the Road to Responsible Competitiveness: ALAFA's Origins

The Lesotho apparel industry, with its 40,000 to 45,000 employees, is an economic mainstay for this poor country. Its existence is fragile, however, because wages (at least \$100 a month) are twice what they are in competing Asian nations such as China. The manufacturers are largely transplanted Chinese and Taiwanese companies that could easily move elsewhere. But the existence of a U.S. law, the African Growth and Opportunities Act (AGOA), has provided a special duty-free entrée into the U.S. market, giving Lesotho a competitive edge. From 2004-2006 the industry was hit from all sides. Most importantly, the international apparel quota system, known as the Multi-Fiber Agreement (MFA), ended in 2005. The result was a tsunami of Chinese exports. At the same time, the value of Lesotho's currency was rising against the dollar. Finally, AGOA's provisions were set to expire in 2007 and 2008. Employment shrank from 54,000 to 40,000, and a half-dozen plants temporarily closed.

The U.S. Congress eventually extended AGOA to 2015, and Lesotho's apparel industry rebounded. Coming up, though, is the 2012 expiration of a key AGOA provision that allows less developed countries like Lesotho to use fabric from the cheapest source, not just from Africa or the United States.

The international effort to recover from the demise of the MFA quotas garnered Lesotho considerable attention and contributed directly to the founding of ALAFA. The MFA recuperation effort became embodied in the MFA Forum, which holds meetings involving governments, international organizations, private corporations, trade unions and nongovernmental organizations. Andy Salm directs the textile and apparel program of ComMark Trust, a nonprofit group funded by the U.K. Department for International Development (DFID). Salm recounts, "We got companies and workers to go to places where the forums were held. This raised Lesotho's profile." ComMark's goal is to restructure and expand certain trade sectors in southern Africa so that they work to alleviate poverty. Salm has been advising the Lesotho apparel industry since 2002.

One of Salm's strategies was to carve out an "ethical manufacturer" niche for Lesotho. "The industry had to clean up its act," says Salm. "We had to assure the international brands that if you bought from Lesotho, there would be no bad publicity — no sweat

shops, no labor law violations... HIV became one of the issues that allow brands to show that they are addressing the well-being of the people in the industry.” Salm and ComMark obtained seed money from DFID and the Lesotho government to launch an apparel factory-based HIV control program. This money went to hire three South African consultants to write a feasibility report on the concept. Also, Dagmar Hanisch was hired as project implementation team leader and remains ALAFA’s director of policy and prevention.

The MFA Forum made Lesotho one of its priorities. In May 2006, ComMark and the MFA Forum hosted an international gathering in Maseru, the capital of Lesotho. The meeting was dubbed “Destination Lesotho: On the Road to Responsible Competitiveness Conference.” It included United Nations (U.N.) and government officials as well U.S. garment brands, local manufacturers and union representatives. A gala dinner at the conference proved to be a suitable occasion to launch ALAFA in the glare of international publicity.

Among the attendees at the conference and ALAFA launch was the singer Bono, who developed the concept of the “Product (RED)” clothing line. Product (RED) corporate members donate part of the profits on their (RED) products to the U.N.’s Global Fund to Fight AIDS, Malaria and Tuberculosis. One Product (RED) member, the U.S. company Gap Inc., agreed to fund an ALAFA pilot program at the 4,500-person Precious Garments facility from which it sources both (RED)- and Gap-branded items. Edun, another Bono ethical apparel spin-off, began producing its own “ONE” T-shirt whose purchase price included a \$10 donation for ALAFA. In November 2006, ALAFA received a \$276,000 check from this source.

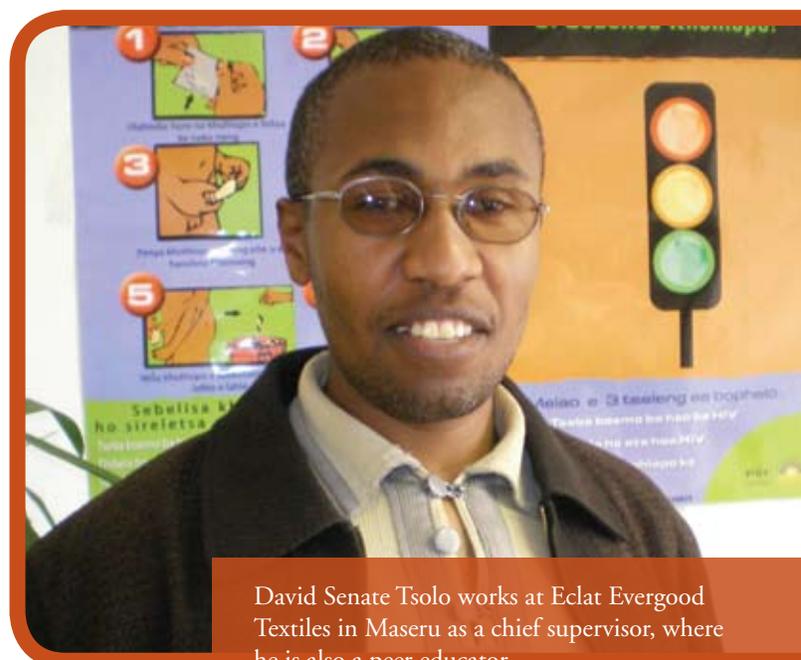
ALAFA Today

Gap and Edun have continued to support ALAFA, with additional support from such U.S. buyers as Levi Strauss, Wal-Mart and Nordstrom. Cathy Dix, Gap’s corporate social responsibility manager for sub-Saharan Africa, says, “Gap Inc. supports the ALAFA program because of its innovative and scalable approach to addressing the HIV/AIDS pandemic. ALAFA is a unique intervention in that it is a holistic, industry-wide initiative covering prevention, treatment and care for those infected with the HIV virus. It is a proven model that has changed the lives of thousands of garment workers, both male and female.” The major portion of ALAFA’s continuing funding has come from the UK’s DFID, with other large grants from the European Union and the Irish government.

Three years after its founding, ALAFA has expanded to 30 factories covering 90 percent of the apparel workforce. That expansion took some convincing. Bart Vander Plaetse, ALAFA’s CEO says, “We started out with the two more-concerned companies, but the buyers encouraged the others to join. The other companies had to see the economic advantages. They now understand that ALAFA creates a healthier and more stable workforce. They see they have a greater chance of getting new orders.” ALAFA’s active support from international buyers and donors also showed the factories that ALAFA was a relatively low-cost way to enhance their sales appeal as ethical manufacturers. The textile and apparel exporters’ association now sits on ALAFA’s two oversight councils along with ComMark, government and trade union representatives, and the international buyers and donors.

Since the apparel industry works with ALAFA in a unified manner, it increases the potential for continuity of HIV care and education. Other workplace HIV programs in the region center on a single large business. The mining companies in South Africa, for example, provide HIV care and prevention services, but only regular employees receive HIV treatment. This leaves out the growing number of workers employed on a contract basis and employees’ families, which are usually distant from the mines. These standalone programs have little impact on community attitudes. Uptake of care is low even among the employees due to HIV stigma and fears of discrimination. Also, individual company programs can offer no continuity if the worker leaves the company’s employment for whatever reason, including ill health.

One factor mitigating some of the impediments is that the Aurum Institute has extended mining giant Anglo American’s



David Senate Tsolo works at Eclat Evergood Textiles in Maseru as a chief supervisor, where he is also a peer educator.

comparatively comprehensive HIV care and treatment program to other workplace and community sites under the auspices of the Aurum Institute. The Aurum Institute was founded by an Anglo American subsidiary but became an independent nonprofit in 2005. Since then, extension of corporate programs to the broader community has become an increasing topic of discussion. That broader community contains about 5.5 million HIV-positive South Africans. At the end of 2008, a mere 5,200 were receiving anti-HIV medications through Aurum's 34 work-site programs, most of them still related to Anglo American.

Testing: The ALAFA program consists of three in-house components: HIV testing, treatment and prevention. Testing is crucial because it provides the link to treatment, which is life-saving. Yet Basotho have shown considerable resistance to HIV testing. A government campaign, called "Know Your Status," has met with only limited success due to underfunding and poor organization. An underlying issue is the stigma attached to testing positive. Salm recalls, "One woman related that her friends treated her like a prostitute when she tested HIV-positive, but those people are all dead now."

At one point in 2008, ALAFA ran a grocery voucher lottery to encourage testing uptake. The workers in the initial ALAFA factories are now 70 percent or 80 percent tested, says Vander Plaetse. ALAFA claims to have tested a total of more than 13,000 apparel workers as of May 2009. That is about 30 percent of the entire workforce.



ALAFA factory, Lesotho Precious Garments

Treatment: The availability of treatment is critical to encouraging testing. When workers see their colleagues dramatically recover after receiving antiretroviral therapy (ART), HIV testing becomes much more compelling. ALAFA originally thought to depend on the government clinics, which dispense free ART. These clinics are distant from the factories, though, and require long waits to see a doctor. A factory employee would lose a whole day's work going to the government clinic. That is something she could ill afford and her employer would frown on.

ALAFA in response instituted a program of factory-based clinics. The manufacturers provide the facility and hire a nurse. ALAFA pays the doctors. By special arrangement, the government supplies ART without charge to these private clinics. The factory clinics also provide a range of general health services beyond HIV — employees do not have to be HIV-positive to make use of them. This feature allows HIV-positive employees to visit the clinics without publicizing their HIV status to the world. (The workers may also see the doctors at their outside offices to ensure that their HIV status is kept private.)

Employees who test positive for HIV are immediately linked to the care available at the workplace clinics. About 85 percent of the people diagnosed with HIV take advantage of these services. ALAFA clinics are available at 20 sites to about three-quarters of the apparel workforce, as of March 2009. They serve 3,500 HIV-positive workers, with more than 900 receiving ART. Median time on ART was only 13 months, again according to the March 2009 report. The treatment program's overall success had yet to be demonstrated at that time.

ALAFA's clinics have implemented the 2008 government guidelines, which specify starting treatment when patients' CD4 counts fall below 350. Patients nonetheless have been starting ART at a median CD4 count of only 173. Patients are still entering treatment in a very debilitated state, which limits the treatment response rate. Presumably, this situation will improve as the treatment program matures. Treatment options are rather limited (mostly nevirapine plus two nucleoside analogs). That said, sharp increases in CD4 counts have occurred. ALAFA, in March 2009, reported that almost 90 percent of all ART-treated workers had attained CD4 counts above 200, the upper limit for an AIDS diagnosis.

Prevention: Peer educators run the ALAFA prevention programs, which cover nearly all garment industry workers. The goal is to train 500 such educators who, in turn, educate their fellow shop-floor employees, a goal that was three-quarters fulfilled by early 2009. The subjects covered in the educators' training include basic HIV and AIDS information, relationship issues, family planning and communications skills.



Peer educators at China Garment Manufacturers factory take time for a lunch time mobilization.

Though generally sexually active, Basotho are usually reluctant to talk about sex, and most of them are Catholic. The HIV education represents a cultural breakthrough, not least because it is largely oriented around women's issues. The material generally follows the ABC approach — abstinence, be faithful, use condoms. Vander Plaetse comments, “We are about to go large scale with a campaign that outlines the risks of multiple concurrent partnerships, stressing A and B messages. But we are realists. Safe sex messages and materials form a large part of our prevention program.”

A major issue is poverty and the resulting transactional sex that women use to get by (to pay the rent, for example). ALAFA's 2007 HIV prevalence survey found that multiple concurrent sex partners (along with sexual transmitted infection symptoms and being the family's sole breadwinner) appreciably increase female apparel workers' risk for HIV.

A major constraint is the apparel workers' cultural roots in an oral tradition, which necessitates the creation of mostly visual or easy-to-read materials. Another problem is the short time periods that the companies allow workers to leave their jobs to attend employee sessions. Many companies try to fit HIV sessions into lunch periods, which is obviously not optimal.

Vander Plaetse says, “We aim at least one big interaction moment in factory. We're getting a meeting once every two months. There are also mixed status support groups. At some factories, these meet every week, whereas in others, they are struggling to keep alive.” ALAFA is attempting to evaluate the effectiveness of its prevention program through a behavior change survey conducted in the first half of 2009. Results will be out later in that year. Vander Plaetse says, however, “I really want to have seroconversion numbers. People who tested negative last year and then seroconverted during our campaigns are a particular challenge — each one is a defeat.” ALAFA's widescale HIV testing will yield information about seroconversion in previously negative testers. To improve future results, ALAFA is organizing posttest clubs to support HIV-negative persons in their efforts to stay uninfected.

A Challenging Economic Environment

Vander Plaetse notes, “We can empower the women for behavior change. Some go back to the homesteads, where the man is still boss. So now we have programs for the men, too.”

A major 2009 move is the expansion of the ALAFA programs to include spouses and children. As Vander Plaetse's comment highlights, a rollout makes sense since the families function as an economic as well as a social and sexual unit. Frequently one



Liapeng Mpeke is a textile worker registered on the ALAFA program and a peer educator at the factory where she works.

member of the couple transmits HIV to the other, with the risk particularly high for male-to-female transmission. The virus can then infect newborns. Losing one of the parents to HIV is a tremendous economic and emotional hardship for the survivors. Having sick and dying children is also a great strain.

This rollout is taking place at a critical time. The South African mines are laying off many Basotho men due to the global economic downturn. Many will need HIV care and prevention counseling upon their return to Lesotho. Basotho garment factories may themselves cut back as the crisis progresses. ALAFA already has provisions to extend health care to laid-off apparel industry workers for six months or more. This interval will allow them to find alternative medical providers without interruption of care, though most will probably end up at the already crowded government clinics.

Fortunately, the first year of the downturn did not affect the Lesotho apparel producers as much as those in other countries. Garment exports to the United States dropped 11 percent, and the industry reduced its total employment by 2,000. “The Lesotho industry has shown a lot of resilience, more than I expected,” says Salm.

There is also the question of whether the international brands and other donors will be able to continue to support ALAFA at present

levels. Salm remains confident. He says, “As long as industry is there and donors support it, the program will stay in place.

It’s a cost-effective way to deal with HIV, but it’s not within the factories’ capacity to pay for. The competition in this industry is cutthroat.” But ALAFA’s mainstay grant from DFID ends in 2011. Replacement funding is not yet apparent.

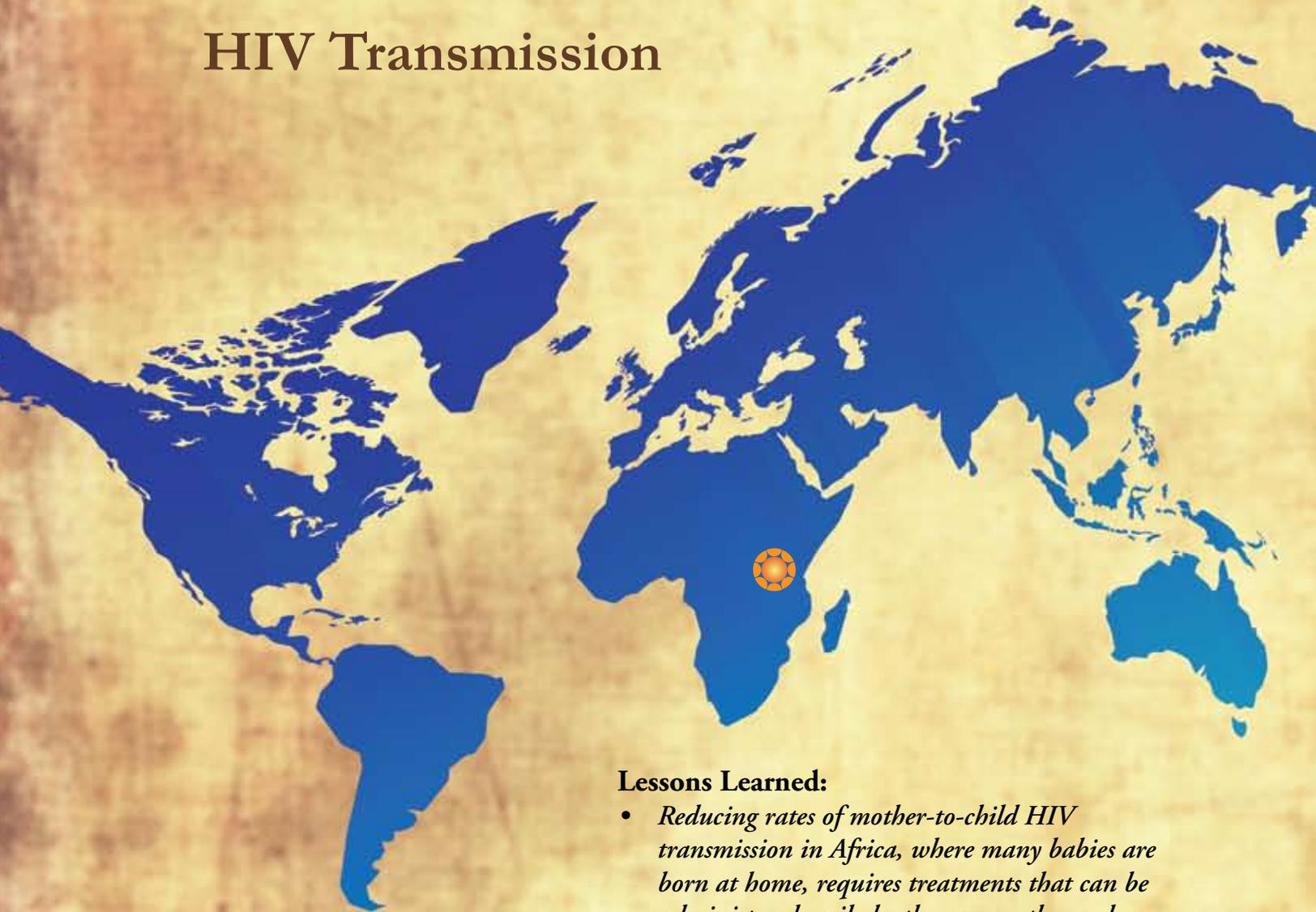
The Lesotho government is the supporter of last resort since it will have to deal with the HIV epidemic if ALAFA doesn’t. David Rantekoa, formerly Lesotho’s principal secretary of trade and development and now ambassador to the United States, was instrumental in bringing the parties and resources together that founded ALAFA. He says that the government is committed to ALAFA’s program: “The government strongly believes that textiles are the driver of the economy, and it is absolutely crucial to pay attention to [the] well-being of workers in that industry.”

The Lesotho government’s proposed 2009-2010 budget calls for a 55 percent increase in health expenditures. It is difficult to exaggerate the low level at which the government is starting. The latest World Health Organization country report for Lesotho — issued in 2005 — described a grossly overstretched health system about to face the daunting burden of AIDS. Per capita health expenditures were only \$28, and there was only one doctor for every 16,400 Basotho. Lesotho’s economy has grown considerably since then and so has the national health budget. Yet the 2009 health appropriation would still amount to only about \$80 per person. Lesotho remains one of the poorest countries of the world, much poorer than neighboring South Africa but with an HIV crisis of equal extent.

ALAFA’s workplace strategy represents an efficient way to combat HIV in Lesotho and other poor countries with a concentrated industrial sector composed of medium-sized corporations. These companies are unable to develop HIV programs on their own although they have economic and public image reasons to do so. ComMark is considering transplanting the ALAFA model to Swaziland, another very poor country with a textile industry looking for an edge in its competition with South Asia. Yet the question of the model’s sustainability remains — securing stable funding will be critical in the years ahead.

By David Gilden

Nevirapine Single-Dose Packs Improve Protection from Mother-to-Child HIV Transmission



Lessons Learned:

- *Reducing rates of mother-to-child HIV transmission in Africa, where many babies are born at home, requires treatments that can be administered easily by the new mother or her birthing assistant, outside of a hospital or health care facility.*
- *Simple technical changes in packaging can increase access and usage of needed medication.*
- *Collaborations between corporate drug developers and nonprofit organizations combine the dual need for research and advocacy to achieve these technical changes.*



Nurse Emily puts the dispenser into the sealable package, where it will stay clean and protected for weeks, until needed. Written and pictorial instructions on the package make it easy for a mother or her birthing assistant to use.

Photo provided by PATH

In resource-restricted settings, nevirapine is a critical drug for preventing mother-to-child HIV prevention (PMTCT) during labor and delivery. HIV-positive mothers take a tablet early in labor and give a liquid formulation orally to the infants within 72 hours of birth. In Africa, many fewer babies than mothers receive their dose. A major obstacle has been the lack of individually packaged doses of liquid pediatric nevirapine. The large number of women who give birth at home should be given such doses during antenatal clinic visits. A collaboration among PATH, the United States Agency for International Development (USAID), nevirapine producer Boehringer Ingelheim, the Elizabeth Glaser Pediatric AIDS Foundation and the Kenya Ministry of Health set out to develop a simple nevirapine delivery system for newborns.

The initial idea was to prepackage single pediatric nevirapine doses at a central facility. This effort failed due to limited shelf life and regulatory issues. Ultimately, the collaboration developed a self-sealing laminated foil pouch designed to hold a capped oral syringe. Clinic staff members fill the syringe with nevirapine, cap it, seal it in a pouch and instruct their antenatal patients on how to use it. Health care workers and expectant mothers have welcomed the innovation. Initial signs are that more at-risk babies are receiving nevirapine. This project is contributing to the UNICEF efforts to develop a take-home mother-baby pack. The new pack would hold a more potent and prolonged combination PMTCT regimen.

Project Origins

“In 2001,” recalls Adriane Berman, senior program associate at PATH in Seattle, “after conversation with colleagues at Boehringer Ingelheim and Population Services International, USAID approached PATH on ways to more effectively deliver infant nevirapine for preventing mother-to-child HIV transmission.



Photo by Shutterstock® Images

This was part of an ongoing conversation between USAID, the Boehringer Ingelheim pharmaceutical company and Population Services International.” And so began a five-year international quest leading to a simple, practical step forward in the struggle to control the HIV epidemic.

The beginning of this decade was a breakthrough epoch for bringing HIV treatments to developing countries. The first step, PMTCT, was a more tractable issue than treating established HIV infection. The U.S. National Institutes of Health trial HIVNET 012 pointed out an elementary strategy in 1999: Vertical HIV transmission could be reduced by 41 percent merely by giving the mother 200 mg of the anti-HIV drug nevirapine during labor and a small liquid dose to the newborn. (Single-dose nevirapine achieved this reduction at month 18 after birth. The reduction was in comparison with multiple doses of AZT given to the mother in labor and baby in the first week. All of the mothers breastfed their babies.)

In response, Boehringer Ingelheim, the manufacturer of nevirapine (brand name Viramune®), announced its PMTCT donation program in July 2000. Extended indefinitely after the initial five-year span, the program supplies low-income countries unable to secure a purchased nevirapine supply.

Groups such as USAID and Boehringer’s program administrator Axios International soon noticed that, although the program was successful at reaching those who give birth in urban or district clinics, it was much less successful in rural areas where many women give birth at home. For example, the Elizabeth Glaser Pediatric AIDS Foundation reported that at 10 African clinics, two-thirds of HIV-positive mothers received single-dose nevirapine from 2000 to 2003, but only about half their babies did.

Less than half the mothers in sub-Saharan Africa give birth in a clinic, and Berman says, “In some places, the government and the doctors didn’t trust women to take drugs home, or they didn’t have the supplies to do it.” In addition, it was easy to hand out a single nevirapine tablet for the mother. The newborn’s dose — which is supposed to be taken within 72 hours of birth — was initially 0.2 ml/kg of a viscous liquid formulation. That was eventually simplified to 0.6 ml fixed dose for take-home use. Pediatric nevirapine comes in 240 ml and 20 ml bottles, so measuring out the small individual quantity, packaging it and storing it at home was extremely cumbersome, as was administering it to the baby. At this stage, suitable packaging was not available.

The lack of nevirapine uptake helped perpetuate the overall limitations in HIV care. “The beauty is that if you offer something, people add other things. More and more mothers are covered in remote areas. In general, the coverage of babies increases,” says Michael Rabbow, director of Boehringer’s PMTCT-oriented Viramune Donation Programme. The existence of the nevirapine program encourages a more geographically dispersed clinic network, more frequent antenatal visits and ancillary services such as nutrition support.

Seeking an Elegant Solution

PATH’s formal undertaking to develop a take-home single-dose nevirapine delivery system began in 2002 with USAID funding through the HealthTech: Technologies for Health Program. As the project developed, USAID was able to provide advice and feedback from its network of field offices. It also contributed to key decisions and provided PATH with connections to outside organizations, including the World Health Organization (WHO), U.S. Pharmacopoeia and other USAID-funded projects capable of advising on the concept. Playing a more active role was Boehringer Ingelheim. “Boehringer was the only company with approved nevirapine [at the time], and the company didn’t want to release the technical dossier,” says Berman. “Boehringer did the stability testing. It was providing the drug free and was a critical partner all the way as we moved to see what would work in field. At each step, the company advised on what it would support.” Boehringer receives little revenue from nevirapine because nearly all sales are by low-cost generic manufacturers in developing countries, which Boehringer allows despite its patents.

PATH's original idea was to provide clinics with a prefilled oral squeeze bottle or syringe at a cost of less than 20 cents per unit. The hope was that the unopened prefilled applicator would not only be a great convenience for clinic staff, but would also extend the drug's shelf life. Boehringer currently rates the shelf life of a large unopened bottle of liquid nevirapine as three years. That figure goes down to six months once the bottle is open — if kept below 30° C. In Boehringer's tests, the nevirapine in the individual-dose containers was stable for just two months. The problem was that the individual-dose containers had considerably more plastic per unit of drug compared with the large multi-dose bottles. The plastic absorbed some of the preservative in the nevirapine formulation.

In December 2004, Boehringer informed PATH that it could not go ahead with the centrally prefilled scheme. A major problem was that extending the shelf life of the individual-dose units necessitated reformulating the oral solution. Besides the investment in creating and testing the new formulation, this change would have required new regulatory approval. In any case, creating a facility to fill an altered packaging format meant substantial investment in infrastructure by either Boehringer or the recipient countries. Regulatory approval would be necessary here too.

Adapting to a Practical Solution

Meanwhile, a few Kenyan clinics were moving ahead with their own makeshift solution. They removed the needles from standard intravenous syringes, siphoned into them sufficient nevirapine liquid and packaged them in the materials at hand — multiple layers of aluminum foil, plastic bags and paper sheets plus used medication boxes. When those materials were not available, the mothers frequently did not receive any nevirapine to take home for their newborns.

Boehringer made a step forward in 2005, when it began shipping empty oral syringes along with the bottles of infant nevirapine. The availability of standard syringes did not by itself ensure a take-home newborn dose, however. PATH revamped its effort by focusing on packaging the syringes. Inspired by the Kenyan makeshift model, PATH proposed a laminated foil pouch with a self-sealing adhesive strip. The pouch provided an area for a printed label containing pictorial instructions and space to write the expiration date. PATH found a manufacturer that would produce the pouch in quantity for 8.5 cents each. It then designed a pictorial label and published a manual for training health care personnel.

Simple as the oral syringe in a self-sealing pouch is, it still has several drawbacks. The major one is that it requires individual filling at the point of use rather than at a central mass-production facility. This is inconvenient, and it was uncertain at first whether health care personnel would embrace the process on a wide scale.

A major disappointment was the two-month shelf life, which the sealed pouch did not prolong. If a pregnant woman has her only antenatal clinic visit before the 32-week point, she may not receive the nevirapine dose for her baby. Kenya and some other countries are taking a more aggressive approach. They are giving the newborn's nevirapine to the pregnant woman whenever she comes and ask that she return for a new dose in two months, believing that something is better than nothing in any case, despite the shelf life issue.

From Field Evaluation to Field Availability

It was therefore unclear what reception the syringe pouch would encounter. But a USAID 2005 survey of PMTCT program managers in Kenya and PATH on-site visits showed that the pouch was widely regarded as an improvement over the existing situation. The Elizabeth Glaser Pediatric AIDS Foundation, the Kenyan Ministry of Health and Family Health International then conducted formal field evaluations that had extremely positive results.

“Our impression was that people were really excited,” says Nicole Buono, who is project director for Elizabeth Glaser's Global Call to Action, which promotes PMTCT. “The providers were more comfortable with sending drugs home. The reality is deliveries happen at home, and people might not come in for weeks. Without the pouch, nurses have to bundle up the nevirapine themselves and give instructions.”

A September 2006 stakeholders meeting in Kenya reviewed the studies. The enthusiasm was so great that the Kenya Ministry of Health promptly changed its guidelines to recommend distributing take-home infant nevirapine packaged in the syringe and pouch. PATH provided a year's supply of the pouches to cover the rollout program. With PATH and Elizabeth Glaser advocating for wider distribution, Boehringer soon agreed to add the pouches to its donation program. Says Rabbow, “Once the pouch was designed and field tested, we knew we should add it to our package, and I knew we could pay.” Boehringer's shipments began in November 2007 and totaled more than 260,000 through early 2009. The company sent a similar number of syringes in the same period, although Buono recalls occasions when transport delays prevented either the pouches or syringes from arriving with the nevirapine supply.

It is difficult to evaluate the effect of the pouch on infant nevirapine use at this writing (April 2009). Widespread pouch availability did not occur until 2008. Rabbow points to a progress report from Zambia's Center for Infectious Diseases, which states that infant nevirapine coverage increased from 58 percent to 77 percent after the pouch arrived. Marie-Hélène Besson, who administers the Viramune Donation Programme at Axios

International, notes, “We will never reach 100 percent nevirapine coverage because some mothers are not convinced it is helpful; there is fear and stigma, family pressure.”

Future Developments

This project was successful because the partners complemented each other’s capabilities. PATH has long experience developing alternative health technologies feasible in resource-restricted environments. The Elizabeth Glaser Foundation had relationships with the Kenya clinics so that it could introduce the pouch and survey the reaction to it. The Kenya Ministry of Health incorporated the new packaging into its official HIV guidelines. Boehringer Ingelheim, most importantly, already had a wide, free PMTCT distribution system in place. Finally, PATH and the Elisabeth Glaser Foundation had the advocacy skills to convince the drug company to ship the pouch along with the nevirapine.

Berman concludes, “Where we ended up is not where we thought we would go. But we ended up with a simple approach — syringe, pouch, instructions — that facilitated sending the drug home.”

Nonetheless, many improvements could be made. A first step is to increase coverage. A major possibility is to work with the home birth attendants that help many mothers deliver. Besson says, “The pouch has provided opportunity for clinics to be in contact with traditional birth attendants [TBAs]. Some clinics have regular meetings with TBAs and can provide the pouch to women who did not come to the clinic late enough. This cooperation, which started in Tanzania five years ago, is now more and more common. These are programs beyond nevirapine distribution. Still, TBAs may be most appropriate channel for extending this distribution.” PATH is already working on a small box of critical birth supplies for home-birth attendants, and that kit could easily include drugs for HIV.

PMTCT does not stop with nevirapine. The current WHO guidelines recommend a combination preventive regimen. If the mother is not already on antiretroviral therapy for her own health, she is supposed to receive AZT starting at week 28 of pregnancy, and then single-dose nevirapine plus AZT during labor. Her infant is supposed to receive single-dose nevirapine at birth and then one week of AZT. A Thai trial found that this combination reduced mother-to-child transmission by 80 percent compared with administering AZT alone to both mother and child (all infants were formula fed). UNICEF is now working on a mother-baby pack that would provide the WHO regimen and supplemental medications in a single take-home box. PATH and the Elizabeth Glaser Foundation are both consulting on the UNICEF project.

The nevirapine pouch took five years to bring to fruition, but it is now leading to further innovation. Projects that facilitate PMTCT have great potential to reduce infant HIV prevalence in resource-restricted areas even without the extensive use of combination antiretroviral therapy seen in North America and Europe. Mother-to-child HIV transmission rates in developed countries are about two percent. In Africa, Botswana has achieved rates only a little higher following the WHO guidelines. This success is predicated on Botswana’s rapidly growing PMTCT program, which is integrated into Botswana’s extensive perinatal care program. As a result, more than 95 percent of HIV-positive pregnant women receive PMTCT medications.

By David Gilden

NATNETS Succeeds in Controlling Malaria in Tanzania With Effective Public, Private and Nonprofit Partners



Lessons Learned:

- *Recognizing each partner's expertise and value is crucial in a large-scale collaboration.*
- *Monitoring and evaluation lead to established best practices.*
- *Working locally with partners is a valuable way to test ideas and develop best practices, which can later be applied to a broader geographical area.*



Photo provided by the National Malaria Control Programme, Tanzania.

Malaria is the overall leading cause of death in Tanzania with approximately 36 of 38 million Tanzanians at risk of contracting the disease. Health care and treatment for malaria, along with decreased economic productivity and opportunity, costs the nation an estimated \$119 million per year, 3.4 percent of gross domestic product. For Tanzania, malaria is not only a health issue, but a development issue.

To control malaria, which is transmitted by *Anopheles* mosquitoes, Tanzanians — especially pregnant women and children under five years old who are most vulnerable to the disease — are encouraged to protect themselves with insecticide-treated bed nets.

NATNETS, a collaboration of government, private and nonprofit agencies, with the goal to plan and implement a national strategy to increase the use of insecticide treated nets (ITNs) in Tanzania, used the successes of partners' past programs and utilized the roles of each organization to establish a successful and growing malaria control program.

Led by Example

To develop NATNETS, organizers reviewed results from previous bed net operations. The Kilombero Net (KINET) project operated in two districts in the Kilombero Valley from 1996 to 2000. The Ifakara Health Institute, formerly Ifakara Health Research and Development Centre, and the Swiss Tropical Institute, with support from the London School of Hygiene and Tropical Medicine, implemented the bed net distribution program. The KINET project showed an association between regular use of ITNs and a 27 percent reduction in child mortality, as well as a 60 percent decrease in childhood anemia. ITNs also proved to have a positive impact on reducing malaria in pregnant women.

KINET not only showed bed nets could control malaria under such a program; it also generated initial social marketing experience and tested an innovative voucher system. Pregnant women were given a voucher that allowed them to buy a net at a discounted price in participating shops.

In addition to KINET, Population Services International's (PSI) Social Marketing for ITNs (SMITN) project operated in four



Photo provided by the Tanzanian National Voucher Scheme (TNVS) partnership.

Establishing ITN Policy in Tanzania

With the formally established national policy, SMITN became a national program and was renamed SMARTNET in 2002. SMARTNET went further than the original program. It dropped procurement and distribution of its own subsidized ITN brand, called Njozi Njema, and started supporting brands owned by the local net industry. The private sector was brought more into the partnership.

While KINET and SMITN had inhibited the development of local distribution networks because the commercial sector could not compete against subsidized products, net manufacturers could now rapidly develop their own brands. Under SMARTNET, a memorandum of understanding was established with net manufacturers. They would be provided with free insecticide kits if they agreed only to sell nets bundled with kits. Manufacturers and wholesalers were provided with transport subsidies to ensure nets were available in remote areas, and retailers were also recruited to participate by stocking nets.

SMARTNET, like SMITN, included an important behavior change component that stressed the importance of nets in preventing malaria and encouraged Tanzanian residents, especially pregnant women and children, to use nets diligently. The campaign messages were released through radio, TV and print marketing, as well as rural films, road shows, posters and roadside signs. Radio proved to be the most effective marketing tool. Multi-brand commercial advertising also increased demand.

In 2003, the government of Tanzania, the Swiss Agency for Development and Cooperation (SDC) and the Swiss Tropical Institute, acting as SDC's executive agency, partnered to develop an ITN cell within the National Malaria Control Program. The Swiss Tropical Institute provided experienced staff and technical support to this cell, and SDC provided funding via the institute. From then on, the ITN cell would be responsible, as a part of the National Malaria Control Program and, hence, the MoHSW, for facilitating and coordinating the NATNETS program's overall management and fundraising.

The ITN cell organized a NATNETS Steering Committee to provide guidance for and oversight of the program in general, and the ITN cell specifically. The committee is chaired by the chief medical officer and includes the director of preventative services, the national malaria control program manager, the ITN cell team leader and representatives from the Swiss Tropical Institute; the DFID; the Dutch embassy; United States Agency for International Development, under the President's Malaria Initiative; Population Services International; the Global Fund to Fight HIV/AIDS,

additional regions from 1998 onward. With funding from the United Kingdom Department for International Development (DFID) and the Royal Netherlands Embassy, a classic social marketing program introduced two new brands of ITNs, including heavily subsidized nets for pregnant women. SMITN also developed and marketed subsidized insecticide re-treatment kits, a highly innovative development that offered a new method to promote net re-treatment.

In October 1999, a group of stakeholders from the public and private sector met to discuss the success of these projects and the urgent need for a national ITN policy in Tanzania. As a result of this meeting, in 2000, the Ministry of Health and Social Welfare (MoHSW) of Tanzania commissioned the development of a national ITN policy. This policy was developed by the National Malaria Control Program, the UNICEF and the Swiss Tropical Institute, discussed by national stakeholders in August 2000, and approved by the MoHSW in December of that same year, thus creating a national strategic program for scaling up the use of ITNs in Tanzania called NATNETS.

Tuberculosis and Malaria (GFATM); Local Fund Agent (PWC); UNICEF; and the World Health Organization (WHO). The committee meets quarterly, more often if necessary.

Membership of the Steering Committee changes periodically to reflect the changes in the donor partnership. With the launch of the President's Malaria Initiative and the World Bank's Malaria Booster Programme, both organizations were invited to join the Steering Committee, while the UK's DFID discontinued its membership upon the conclusion of the SMARTNET program.

The Tanzanian National Voucher Concept

Don de Savigny of the Swiss Tropical Institute came up with the idea to create a voucher system to distribute insecticide-treated nets. De Savigny, along with Alastair Unwin of the UK's DFID and the National Malaria Control Program, developed a proposal for the plan and brought it to NATNETS partners.

In June 2003, after successfully securing the first grant funded by the GFATM, the MoHSW contracted Mennonite Economic Development Associates (MEDA) to design a voucher system for the distribution of insecticide-treated nets. Following the design of the Tanzanian National Voucher Scheme (TNVS), MEDA was contracted to implement the program.

MEDA, the logistics contractor for TNVS, which has been involved in the insecticide-treated net sector in Africa since the early 1990s, prints and delivers vouchers at the national level through the Tanzanian health system via 4,432 clinics.

Initially, every pregnant woman received a voucher at the time of her routine checkup. In 2005, the President's Malaria Initiative joined NATNETS to fund an infant voucher, which was introduced the following year. Vouchers are given to a child's mother or caregiver when a child is brought to a clinic for measles vaccination at nine months of age.

Pregnant women and mothers can use vouchers in any participating shop for a \$2.50 discount on a treated net. Retailers, in turn, redeem vouchers for more nets from wholesalers. Wholesalers are reimbursed the value of nets by the project or by manufacturers, in the form of more nets. Four net manufacturers, A-Z Textiles, Sunflag, Moshi Textile and TMTL, participate in the TNVS, and 250 wholesalers and 6,900 retailers are registered by MEDA to accept TNVS vouchers. To date, more than 4.9 million vouchers have been redeemed.

Contractual partners, who were originally selected by the government of Tanzania's Central Tender Board under competitive tender in 2003 and 2004, implement the TNVS. MEDA manages the logistics of the program. Net-use training and promotion is handled by World Vision Tanzania, with assistance from CARE Tanzania during the first 18 months. The London School of Hygiene and Tropical Medicine and the Ifakara Health Institute oversee monitoring and evaluation. A financial audit is conducted by KPMG.

Playing Catch-up

In 2007, after much debate, ITN stakeholders decided to launch a new campaign, the Under Five Catch-up Campaign (U5CC), to bring long-lasting insecticidal nets to every child in the country. The new campaign was made possible through an extension to the Round 1 grant to Tanzania from the GFATM. In addition, the World Bank gave a \$25 million soft loan to support the campaign, as well as a National Net Re-treatment Campaign in 2007. As a result, the World Bank joined the NATNETS Steering Committee.

The U5CC received additional support from the President's Malaria Initiative and UNICEF, which received funding for the program from the U.S. charity Malaria No More. The coordination of the U5CC rests within the ITN cell, on behalf of the MoHSW, through policy, grant management and supervision, and contractor oversight.

For this campaign, which is currently under way, 7.2 million long-lasting insecticidal nets made in Tanzania (Olyset™) are distributed



Tanzanian Prime Minister Hon. Mizengo Pinda gives long-lasting insecticidal nets to children under the age of five, as part of a pilot program of the Under 5 Catch Up Campaign in the Mpanda district.



Photo provided by the NATNETS partnership.

to families with children who are under five years old. The nets remain treated with insecticide for at least five years. Because the manufacturer is local and responsible for distribution down to the village level, local logistics are well-handled.

On a district level, the prime minister's office and regional and local governments are responsible for the implementation of the program. Village and ward executive officers register eligible children and organize distribution locally. They follow training by World Vision Tanzania and coordinate net deliveries through MEDA, who works with A to Z Textile Mills, the net manufacturer.

Other implementing contractors include, CARE Tanzania, the Ifakara Health Institute, the London School of Hygiene and Tropical Medicine, and KPMG. PSI and The Johns Hopkins Bloomberg Center for Communication and Programmes implement a supporting behavior change campaign.

Maintaining a Multi-Sector Partnership

The NATNETS Steering Committee manages the program at the policy and strategy level and meets quarterly. Members also hold ad hoc meetings as issues arise. On the implementation level, contractual partners meet monthly to discuss project development. Additionally, a quarterly publication, *NATNETS News*, provides a link to partners and Tanzanian stakeholders.

Government participation in the partnership was critical to the program's success. The Tanzanian government supported the public-private partnership approach, exemplified in the

SMARTNET program. It also supported NATNETS submission of the Global Fund Round 1 proposal that secured funding for the TNVS. Government also played a key role in the implementation of TNVS, by distributing vouchers through reproductive and child health clinics.

An important element of the partnership's success is the established understanding of the need for monitoring and evaluation. Ifakara Health Institute and the London School of Hygiene and Tropical Medicine fulfill this role since joining the partnership in 2004. At first, members were uncomfortable with being evaluated but were persuaded when they realized monitoring helped determine best practices.

For example, the evaluation of delivery strategies was taken to NATNETS stakeholders and discussed by Steering Committee members to determine which approach held the most promise for the program's future.

Clear lines of communication among partners were crucial to the partnership's success. Strategic and implementation issues are discussed regularly and openly by partners to ensure each has his or her voice heard on matters relating to the project's operations and future planning. Recognizing each partner's expertise and finding value in his or her perspectives is crucial to the success of this large-scale partnership.

Moving forward, NATNETS is focused on two campaigns, the U5CC, taking place now and scheduled for completion in early 2010, and the Universal Coverage Campaign, scheduled for the remainder of 2010. The goal of the Universal Coverage Campaign is to provide a long-lasting insecticidal net for every sleeping space in mainland Tanzania by distributing more than 14 million nets. In the last quarter of 2009, long-lasting insecticidal net vouchers will be introduced to pregnant women and infants and will provide a continuing means to deliver them to newly pregnant women and infants.

Organizers are aware that demand for new nets will decline in the immediate aftermath of the Universal Coverage Campaign, and it is not known how this will affect the willingness of retailers to stock nets as they try to anticipate changes in the marketplace.

In the long-term, as existing nets wear out, there will be an extensive consultative process conducted zone by zone among all stakeholders to identify policy and distribution options for distributing new nets and laying the foundation for a future "keep-up" strategy.



Photo provided by NetsforLife®

NetsforLife Utilizes Local Channels to Promote Net Culture in Zambia

Incidents of malaria in Zambia have nearly tripled over the past 30 years. In 1976, the incidence rate was 121.5 cases per 1,000. The numbers rose to 398.8 per 1,000 in 1998 and 428.0 per 1,000 by 2003. In 2006, with hospital visits to treat the infectious disease on the rise, it was estimated that 50,000 deaths per year were attributed to malaria.

Following a pilot program in rural Zambia (funded by ExxonMobil) in 2005 and the publication of the proof of concept, the *NetsforLife*® program partnership was founded in 2006. A unique consortium of funding partners conceptualized, vetted, promoted, blessed and launched *NetsforLife*® with the lead corporate partners of ExxonMobil Foundation, Standard Chartered Bank, Coca-Cola Africa Foundation, Starr International Foundation, White Flowers Foundation and Episcopal Relief & Development as both a funding and implementing partner. *NetsforLife*® distributes long-lasting insecticide-treated nets (LLITNs) and trains people in remote communities about the

protective value of LLITNs, how to use them correctly and how to recognize malaria symptoms and when to seek medical treatment.

The initiative works to instill a “net culture” in sub-Saharan Africa by promoting communitywide understanding of and knowledge about the transmission of malaria and the need for prevention. *NetsforLife*® operates through faith-based organizations established in remote communities where transportation is limited

Faith-Based Approach

In remote Africa, churches are often the only functioning institutions and a primary source of social services. Church leaders are held in high regard and have the presence and power to unite communities. The *NetsforLife*® partnership is committed to utilizing these established and trusted networks on the ground.

NetsforLife®’s success in closing the gap between ownership and use is attributable to its unique ability to engage church leadership in emphasizing malaria messaging and in recruiting church members as volunteer Malaria Agents. These agents are trained



Photo provided by NetsforLife®

through *NetsforLife*® and are the first line of defense in mobilizing communities and promoting awareness to reinforce a net culture. The high-quality training provided to the Malaria Agents and extensive follow-up the agents perform are critical to establishing their high levels of ownership and use in *NetsforLife*® communities. This community-level investment, anchored in the local church, facilitates sustainability and capacity building.

Corporate Approach

The original mix of partners purposefully included private-sector players who could inject business savvy, bottom-line mentality and intense focus on quality and results. Dr. Steven Phillips of ExxonMobil notes Episcopal Relief & Development, as a faith-based organization, was eager for corporate partners to participate beyond financial sponsorship; to contribute to business core competencies, such as assistance with on-the-ground employee engagement, marketing and communications; and monitoring and evaluation. He said one of the most valuable aspects of this part of the collaboration was the ability to establish a corporate-style system of monitoring and evaluation, something not common in partnerships he'd seen before.

Phillips explains that, too often, programs operate without measuring results. The ones that do measure often fail to get data into the hands of the right people, such as donors, program managers, fieldworkers and the communities in which programs are run. From a business perspective, monitoring and evaluation are critical in that they provide a sense of accomplishment, induce further commitments and help determine next steps as well as best practices.

“It creates a virtuous cycle of increasing support and better performance,” Phillips says. ExxonMobil specifically funded a monitoring and evaluation model in each of the African countries.

Seven Million Nets by 2012

The collaborative malaria prevention program began in 2006, in eight countries. In 2009, a milestone delivery of one million nets across 17 countries was met. The primary *NetsforLife*® objective is to distribute seven million nets in 17 sub-Saharan Africa countries by 2012.

The successes of the program come from many levels of collaboration among partners with various areas of expertise. The *NetsforLife*[®] consortium is overseen by an executive board that approves budgets, helps secure funding, defines communication strategies and identifies potential partners. A steering committee comprised of one representative from each partner organization meets quarterly to gather each partner's input on the board's decisions and to discuss operational issues.

The *NetsforLife*[®] initiative's next challenge will be to meet the demand that has been created for nets and education, while adhering to established methodology and upholding monitoring and evaluation standards. Program developers realize the initiative's presence is still very small in proportion to the problem.

NetsforLife[®] serves people in need regardless of faith affiliation or membership within the churches from which it operates. An integrated community development model allows the people of the remote African communities to be involved in the process of education and net distribution.

By Ashley Mastandrea



Photo provided by NetsforLife[®]



Nontraditional Global Health Partners Team Up to Fight Malaria in Uganda



Lessons Learned:

- *Due to the similarity of symptoms, incorrect diagnoses of diseases are common and contribute to the growing resistance to front-line drugs.*
- *Building medical infrastructure in the developing world may be critical to treating epidemic diseases, even if drugs are available.*
- *Keep training local to reach nontraditional health care providers and build developing world medical infrastructure.*
- *It can be critical for a developing organization to diversify funding sources, once it has established its relevance in the early years.*
- *Strong relationships among local and international partner organizations are critical factors in establishing credibility and ensuring wide program participation.*



Anopheles mosquito

Photo by Shutterstock® Images

The Infectious Diseases Institute is gaining international prominence; can the lessons learned to fight AIDS be used in treating malaria and vice versa?

Malaria is a devastating disease that claims a child's life every 30 seconds and kills more than one million people each year. In sub-Saharan Africa, which accounts for more than 90 percent of all malaria cases worldwide, the disease is particularly brutal on the young; there, malaria is responsible for nearly 20 percent of all deaths in children under the age of five.

World leaders have come together with a comprehensive plan to eradicate malaria by 2015 and have pledged \$3 billion to meet this goal. In addition to providing research funding for a vaccine, the plan aims for a reduction in deaths in the next two years by providing mosquito nets, indoor spraying, diagnosis and treatment.

"Several organizations have made a claim that if everyone in malaria endemic zones had a bed net, we could eradicate the disease. I wish it were that simple," says Carol Spahn, executive director of Accordia Global Health Foundation, a nonprofit working to overcome the burden of infectious diseases by building health care capacity and strengthening academic medical institutions in Africa.

Could malaria be eliminated simply by expanding the use of bed nets? "The answer is no. The reason is, mosquitos can still bite you when you're not in bed," says Alex Coutinho, M.D., M.P.H., executive director of the Infectious Diseases Institute (IDI), Accordia's flagship program in Kampala, Uganda.

Bed nets are one very important piece in the arsenal of proven interventions that can help prevent malaria. Others include indoor insecticide spraying and intermittent preventative treatment for pregnant women. But clinical training to enhance the quality of care and counseling is an equally essential component of any effective prevention strategy.

Recognizing this reality, Accordia, ExxonMobil and IDI joined forces over the past four years to create the Joint Uganda Malaria Program (JUMP), an ambitious partnership that also includes I-Tech, Makerere University, University of California San Francisco, the Uganda Malaria Surveillance Program and the Ugandan Ministry of Health. The JUMP program is aimed at reducing the burden of malaria by implementing innovative training approaches that teach health care workers to correctly diagnose malaria. The team-based training has shown dramatic results in improving fever case management and reducing the over-prescription of antimalarials — thereby reducing the problem

of drug-resistant malaria — and building the capacity of Uganda’s health workforce.

“The reason why an energy company is involved in a global health partnership follows a multi-step logic,” says Steven Phillips, M.D., M.P.H., medical director for Global Issues and Projects at ExxonMobil. “First of all, ExxonMobil has a large footprint in Africa. We’ve been on the continent for more than 100 years, and we’ve been present in 25 sub-Saharan countries historically,” he says, noting that ExxonMobil now does business in six countries there.

Additionally, investment in oil and gas resources in Africa has been growing. Africa now represents about eight percent of the world’s oil supplies, but that number is expected to grow to about 12 percent.

“Starting in about 2001, we developed a very comprehensive workplace malaria control program. However, we have to address the reservoir for mosquitos, which is [all] human beings, not just company people,” he says.

JUMP is an integral part of ExxonMobil’s overall corporate responsibility program and commitment to the African continent. ExxonMobil has funded the project at the \$500,000 level each year for the past four years, but the company’s overall commitment to the fight against malaria is much larger.

That said, it may be the Ugandan government’s commitment that is the real indicator of the program’s success, as the government has adopted JUMP’s curriculum as a national standard for training health care workers.

The JUMP program has evolved significantly since it was initially developed. “JUMP started as a classroom-based, five-day training program. But we discovered that sites did so much better in terms of health outcomes after we conducted on-site support and supervision visits that we decided that that had to be an essential component of any training,” says Kelly Willis, M.B.A., senior vice president for program development at Accordia Global Health Foundation. “In doing so, we found it was more cost efficient to have peer leaders conduct the courses, so we created a training-of-trainers module, which has proven to be tremendously effective,” Willis adds. As of the end of 2008, the JUMP program had trained 803 individuals in fever case management and effective diagnosis and treatment of malaria.

A Center of Excellence

While malaria has long been a medical problem throughout sub-Saharan Africa, the impetus behind the founding of IDI was not malaria, but AIDS.

In 2001, a group of North American and African physicians, who had experienced the AIDS epidemic firsthand, recognized that Africa lacked the infrastructure to deal adequately with the problem, so they reached out to Hank McKinnell, Ph.D., the former president and CEO of Pfizer, who now is chairman of the board of Accordia.

“The result was what we originally called the Academic Alliance, which quickly became the Accordia Global Health Foundation,” McKinnell says. That group established IDI at Makerere University in Kampala, Uganda. To date, IDI has trained more than 4,500 health care workers from 29 countries in HIV/AIDS, malaria, laboratory practices, research methods and other critical infectious disease topics.

While IDI is an autonomous institution, it is integrated into Makerere University, which, having been founded in 1932, is one of the oldest universities in Africa. “For a long time Makerere was the only university for doctors in the whole of eastern Africa,” says IDI’s Coutinho.

Makerere University, which has a student body totaling around 30,000 students, produces roughly 100 doctors a year. In the medical school, there are 23 professors, as well as 500 undergraduate and 200 graduate students, according to Coutinho.

While IDI’s development and subsequent reputation as a center of excellence are a relatively recent phenomenon, Makerere University has a long and accomplished history, which includes discovery of new diseases like a tumor called Burkitt’s lymphoma, among others.

“The vision for IDI was that the driving force to combat diseases that primarily impact Africa needs to be firmly rooted in Africa, and Makerere was the natural place to locate it,” says Accordia’s Spahn.

The number of IDI’s trainees has grown substantially since its inception in 2004 to around 1,600 trainees in 2008 alone. With this expansion, the training methods have also evolved. In addition to the trainees who come from across Africa to participate in specific training programs, Makerere medical students also cycle through IDI for a two-week period and follow a patient through the clinical care process and into their homes. This is intended to enable the students to understand the patient’s psychosocial and socio-economic circumstances as part of the HIV/AIDS treatment and care process.

Accordia also sends visiting scholars to IDI, to give lectures and do rounds with medical students, Spahn explains. “These scholars play a critical mentoring role with young African scientists doing research at IDI,” she says. In the last four years, IDI scholars have published 71 articles and presented 92 research abstracts at major infectious disease meetings around the world.

While originally focused on AIDS through contributions from Pfizer, ExxonMobil's generous support allowed IDI to expand to malaria research, prevention and care. In the first year of the JUMP program, activity focused on building relationships and jointly developing a comprehensive curriculum for use in multi-disciplinary team training for the care and prevention of malaria. The second year saw the implementation of the core malaria training program and demonstration of the value of its multi-disciplinary team-based approach to malaria training. In 2008, the program was adapted for national scale by adding modified field-based components for facilities with and without laboratory capacity, external funding was secured for program expansion, and the JUMP curriculum was formally endorsed by Uganda's Ministry of Health.

A New Model of Treatment

According to ExxonMobil's Phillips, the company found that the training approaches being developed at IDI for HIV/AIDS could be leveraged to address malaria as well.

"We wanted to develop a module that complemented what IDI was already doing, by developing a new curriculum for training health professionals in malaria and disseminating it, not only in Uganda, but throughout the continent of Africa," says Phillips.

"But how do you test — how do you export — that technique, and make sure that it is generalizable to other parts of Africa? Malaria is a totally different disease, and it's not like you can turn on a dime. You have to spend substantial financial resources and figure out who the curriculum is for. Malaria is primarily taken care of by people who work in very, very remote health centers, by people who have very little medical training," he adds.

Another part of the problem with malaria in sub-Saharan Africa is that, while the disease is readily treatable, resistance has spread, in part because of frequent misdiagnosis. Treatment can take as little as three to five days if the patient is properly treated with drugs like artemisinin, chloroquine or primaquine. "However, the new products are much more expensive, so we have to train the health workers to much higher levels so they don't waste treatment," says IDI's Coutinho. "That's because malaria is a disease that cycles through the body, and, at different phases of the cycle, different drugs are able to block the propagation of the parasite. For instance, chloroquine is able to block it in the blood cells, while primaquine blocks malaria in the liver cells," he continues.

"In a country like Uganda, you can often find shopkeepers, or what you would call pharmacists, filling the need for local treatment, and we need to be sure we work with them so that they dispense treatment in the correct fashion. We need to make sure we constantly teach and train people on the front line," Coutinho says.

Resistance has mainly been a problem in the last decade or so, as doctors have encountered chloroquine resistance in as many as 30 percent to 40 percent of cases. Malaria is often confused with hepatitis or typhoid or one of a number of other tropical diseases when the patient has a fever.

To deal with the problem, the JUMP partnership developed a new field training model to deliver the most effective care for malaria. The model includes a six-day intensive course in advanced care for and prevention of malaria and targets doctors, nurses, clinical officers and laboratory technicians. The JUMP team includes a medical officer, training coordinator or curriculum specialist, laboratory technician, training assistant, data manager and a driver. Once core teams are trained at the institute itself, they return to their home communities to continue training and teaching others. The JUMP team then provides on-site follow-up support.

"We found that the extra investment in providing on-site support helped solidify the training and resulted in a stronger impact," Accordia's Spahn says.

Expanding Activities and Diversifying Resources

Because of the success of the JUMP program, Accordia and IDI hope to pilot the JUMP program outside of Uganda, to demonstrate the model's success in other settings. "The program has been proven to have a positive effect on patient outcomes in Uganda, and we believe it has strong applicability throughout sub-Saharan Africa," says Spahn. "It is imperative that we scale this up as quickly as possible as a part of the broad plan to eradicate malaria and its impact."

Accordia and IDI are also exploring the potential replication of the IDI model in another country. "We are trying to replicate the institute in West Africa, perhaps in Nigeria," Coutinho says. "Tanzania, Zambia and South Africa already have similar institutes, but in West Africa, there are none," he adds.

Additionally, IDI hopes to acquire land for a new building. "We are fundraising and identifying land; we hope to construct a new building very soon, because the demand for training is so huge," Coutinho says. "The new building will be used mainly for training, but we could also use some space for additional research. In just five short years, we have outgrown our space."

As part of its visionary investment in IDI, Pfizer constructed a state-of-the-art facility in Kampala. "The building is something you might find around the corner from you in the United States, with a bustling level of activity," says Lisa Foster, M.B.A., senior director in the corporate responsibility/philanthropy team at Pfizer. The multi-level building comes complete with an award-winning research lab and hosts as many as 40 physicians and researchers from the region at one time, she adds. In addition, the on-site

Infectious Diseases Institute (IDI) and Treatment for AIDS

Establishing new methods of training providers to treat malaria has not detracted from the Infectious Diseases Institute's (IDI) work in combating the AIDS epidemic. In fact, it may contribute to this work. "People who are HIV-positive or have AIDS are more susceptible to malaria," says Alex Coutinho, M.D., M.P.H., executive director of the Infectious Diseases Institute (IDI). "On average, a patient with HIV will survive if they also have malaria, although it may take longer for them to get better. However, if the patient is HIV-positive and pregnant, and gets malaria, the chances of the baby succumbing are much more severe."

While ExxonMobil has funded the Joint Uganda Malaria Program and the IDI's malaria work, the lessons learned are also contributing to efforts to develop training for nurses and clinical officers in integrated infectious disease management, which combines HIV/AIDS, malaria, tuberculosis and other infectious diseases. Accordia Global Health Foundation has recently received a \$12.5 million grant from the Bill & Melinda Gates Foundation to study appropriate models for training lower-level cadres of health workers, who are bearing a significant burden of caring for patients due to the severe shortage of physicians in Africa.

"Over the last 17 years, HIV or AIDS has gone from being a death sentence to a disease that can be treated in some cases for 20 or 30 years," Accordia's Hank McKinnell, Ph.D. says. "We don't have the 20- or 30-year data yet, but we certainly have patients in Africa who have been on treatment for 10 years or more. Today, nobody needs to die from an HIV infection in Africa due to a lack of drugs," he explains, adding that the problem today is a lack of well-trained providers and adequate infrastructure.

computer server is protected from fire or explosion by a heat-sensing device, and the building features an air-circulation system.

"Our clinic treats up to 300 HIV-positive people per day," says Coutinho, adding that the building has 40 rooms, three pharmacies, a records office and one of only six labs in Africa that are certified by the College of American Pathologists.

Despite the fact that Pfizer solely financed construction of the building, it has welcomed multiple partners in an effort to build long-term sustainability. "The many different partner organizations work very well together," says Accordia's McKinnell. "The reason

A Multi-Dimensional Partnership

The JUMP program is a project that involves a multi-level partnership of more than a half dozen organizations. Each JUMP partner brought strategic capabilities to the successful partnership, and had its own reasons to contribute them to the project.

- Accordia sought to broaden the scope of its IDI, adding malaria expertise to the training program there.
- For ExxonMobil, success meant a stronger strategy to overcome the burden of malaria in Africa, proof that a novel approach could work on a larger scale, and lessons it can share with other partners to achieve that impact.
- For Makerere University and the University of California San Francisco (UCSF), the partnership offered opportunities for students and researchers to get involved in a meaningful way, and contribute to the body of knowledge around malaria programs. UCSF provided needed demographic surveillance in the early part of the program.
- The Uganda Malaria Surveillance Program (a joint venture between Makerere University Institute of Public Health, Uganda Ministry of Health and several other academic institutions) used the incremental funds made available through the JUMP program to expand its own surveillance activities.

One of the key lessons learned during the successful concept, design and execution of the JUMP program was that strong relationships among local and international partner organizations are critical factors in establishing credibility and ensuring wide program participation.

for diversifying is that we did not feel it was appropriate for a major institute anywhere in the world to be dependent on a single source of funding. Once established, like any other organization, it has to develop its own funding sources," he adds.

"In the early years, it was very critical that Pfizer provide a solid base of core funding to establish IDI's relevance, so that when the executive director approaches other organizations to ask for funding, donors will be receptive," says Pfizer's Lisa Foster.

By John Otrompke, J.D.

Public and Private Partnership Helps to Set the Standard of Care for Multi-Drug Resistant Tuberculosis



Lessons Learned:

- *Technology transfer of a drug product may require more than sharing intellectual property. Guidance in training, manufacturing and quality control are also critical.*
- *Multi-pronged strategies that address health care infrastructure are necessary when dealing with a pandemic.*
- *Partnering with local physicians and working through local ministries of health to train nurses, doctors and hospital administrators are critical to making a measurable impact quickly.*
- *A strong social support system, like that provided by community-based care delivery, is essential to successful drug-resistant TB treatment in resource-poor settings, where illness and economic factors can prevent patients from getting to where the treatment is being delivered. Non-medical incentives can be effective in convincing patients to comply with medical treatment.*



A child with tuberculosis takes his medication under the supervision of a community nurse in Gugulethu, South Africa.

When a new form of tuberculosis (TB) was raging through the shanty towns in the Northern Cone of Lima, Peru, Partners In Health (PIH) was on the ground trying to find a solution.

“Our group first encountered this in Peru in 1995, but science has known from the earliest days that you have to give multiple drugs to tuberculosis patients or resistance can develop very quickly, probably within the span of about a month or so,” says Salmaan Keshavjee, M.D., Ph.D., then an anthropologist. “As a phenomenon we saw drug-resistant TB in the 1950s and 60s, and there was a big outbreak of it in New York and Miami in 1991 and 1992,” adds Keshavjee, who has since become a physician and is now a senior TB specialist with PIH.

While as many as two billion people have been infected by TB, or one-third of the earth’s population, only about nine million people per year get active TB. The most vulnerable patients are immunocompromised or those suffering from malnutrition, and while patients can live for as long as 10 years with active TB, if left untreated, “It will kill you in the end,” says Keshavjee. “In the

www.casestudiesforglobalhealth.org

meantime, the TB bacillus is destroying part of your lungs and being transmitted to other people.”

The World Health Organization (WHO) estimates that 1.8 million people die every year from TB, making it essential that those with active TB receive treatment. Some patients may develop a drug-resistant form of the disease; these strains require 18 to 24 months of treatment with numerous second-line anti-TB drugs, making treatment and compliance much more difficult. More than 70 percent of patients with the drug-resistant form of the disease can be cured, however the growth of drug-resistant TB is outpacing global efforts to fight it.

The multi-drug resistant form of TB, known as MDR-TB, strikes about half a million people each year, but is still susceptible to drugs, including capreomycin and cycloserine, two second-line therapies made by Eli Lilly and Company. And it is because of this experience that Lilly set out to create the Lilly MDR-TB Partnership, initially to fill the need for these drugs by supplying them at a concessionary price. The partnership also embarked on a transfer of technology program to generic manufacturers in



Lilly transfers its technology to manufacturers in high-burden countries.

high-burden countries, to enable them to produce the medicines locally. It has since evolved into an alliance of partners — private and public health care professionals, academics, patient- and community-advocacy groups, international organizations, and producers of medicines in developing regions — whose aim is to support the WHO goal in treating 1.6 million MDR-TB patients by 2015.

The Lilly MDR-TB Partnership consists of more than 20 global partners, including Partners In Health, the Centers for Disease Control, WHO, the Stop TB Partnership, the International Council of Nurses, the World Medical Association, the International Hospital Federation, the World Economic Forum, the International Federation of Red Cross and Red Crescent Societies, TB Alert, the Advocacy Partnership, the Global Business Coalition, the Global Health Advocates, Hisun Pharmaceutical, Shasun Chemicals and Drugs, SIA International/Biocom, Aspen Pharmacare, Purdue University, RESULTS, and Eli Lilly.

The partnership was created following the Peruvian crisis of the mid-1990s, according to Patrizia Carlevaro, head of Lilly's International Aid Unit. "Doctors Without Borders asked me if Lilly could give them drugs for some former Soviet Union programs. We had these older drugs which were still very effective. I then began to think that we had to do much more than just give drugs and that's when the inspiration for the partnership began."

Lilly distributes the drugs at concessionary prices, but does so through an organization called the Green Light Committee which monitors MDR-TB projects throughout the world so that treatment protocols are correct and more drug-resistant strains don't develop. "We asked the WHO and others to put together the Green Light Committee, to review requests for drugs in order to make sure that the programs were using the drugs correctly to avoid more drug resistance," says Carlevaro.

"The Green Light Committee evaluates applications from countries. As a mechanism, the committee evaluates countries and approves them or not within two months," says Keshavjee, who currently serves as the committee's chair. If a country requires assistance to strengthen its program before being approved, the committee works with it through the process."

The Green Light Committee (GLC) is comprised of representatives from institutions with specific programmatic, clinical, advocacy, scientific and managerial expertise [see sidebar]. WHO is a permanent standing member. It is charged with reviewing applications, providing technical assistance to countries throughout the application and implementation processes, monitoring and evaluating GLC-approved programs to assess their progress and continued adherence to WHO guidelines, and assisting WHO with developing policy to control MDR-TB.

The Stop TB Partnership and WHO raise funds to sustain the work of the committee from national and government-supported agencies, regional and international organizations, nongovernmental organizations, universities, research institutions and other sources. In addition, a cost-sharing mechanism helps support the efforts of the GLC initiative in countries receiving Global Fund grants for work on MDR-TB.

To become a quality-assured provider of TB drugs, drug companies have to go through the WHO prequalification program, a long process that can take two years or more. One of the key components of the Lilly partnership is transferring the technology

Current Members of the Green Light Committee

(as of September 2009)

Members are eligible for participation for a maximum of two years. An open call for membership is disseminated whenever a vacancy occurs, and members are usually drawn from the Stop TB Partnership Working Group on MDR-TB.

Partners In Health — Current Chair
U.S. Centers for Disease Control
Hospital General de "Francisco J. Muniz"
International Union Against Tuberculosis and Lung Disease
KNCV (Dutch) Tuberculosis Foundation
Médecins sans Frontières
State Agency for TB & Lung Disease, Latvia
World Care Council
World Health Organization Standing Member

to manufacture the two key drugs that can cure MDR-TB — capreomycin and cycloserine. Lilly identified four companies in the developing world and gave them the equipment, methodologies and training to produce these drugs as well as the manufacturing and marketing expertise to be able to provide the drugs to the growing number of countries, health ministries and donor agencies in need of these medicines for the TB pandemic. The four countries were those with the highest MDR-TB burden, so that drug supply could be available for the immediate needs of these nations as well as other countries hard hit by this deadly disease.

“The technology transfer was not a transfer of intellectual property per se, because the patent is over, since the drugs are more than 20 years old,” Carlevaro explains. “We give them all the technologies for manufacturing, and expert production technicians went to the local companies to teach them how to produce the two drugs,” she adds.

In addition to providing the transfer of technology, between 2000 and 2008 Lilly has supplied 2.3 million vials of capreomycin and 5.5 million capsules of cycloserine at concessionary prices to the WHO’s program. This has provided the much-needed drugs in the interim before the new companies were up and running.

An Emerging Economy Model

Of nine million cases of TB that occur annually, scientists now estimate that half a million are of the drug-resistant form. The Lilly partnership contributed to the GLC’s enrollment of around 56,000 patients to date, according to Carlevaro. While the disease is spreading faster than it is being treated, some countries like Russia, which have adopted the partnership model as a standard of care for treating the disease, have seen better progress than others.

“Russia has a very well-established health care delivery system, with sufficient physicians, nurses and resources, so our work is more focused on training those physicians,” says Amy Judd, director of program development in the division of Global Health Equity at Brigham and Women’s Hospital. With a grant by the Lilly Foundation, PIH subcontracts with Brigham and Women’s Hospital to administer the program.

“Whenever possible, we partner with local physicians and work through local ministries of health or the ministry of justice for the prison system, to educate physicians in drug-resistant TB diagnosis and treatment and advocate for effective care delivery models,” adds Judd, who notes that, while PIH is involved in other TB work, its partnership with Lilly is mostly limited to Russia.

Because Russia has established multi-drug resistant treatment as a national policy, the partnership may be improving treatment for as

many as 25,000 patients per year, adds Judd. She also notes that the country sees 120,000 new cases of TB per year, of which 20 percent are multi-drug resistant.

“Partners In Health has doctors in Tomsk, Russia, but we’re not directly treating patients any more. Russian health care professionals basically run everything themselves, and since 2003 or 2004, we have been there just as consultants,” says Keshavjee.

Treatment is also more thorough in Russia than in some places, notes Keshavjee. “In our sites in Russia, patients start in the hospital and then are sent back to the community. With drug-susceptible tuberculosis, patients become noninfectious in two weeks to one month, but for the drug-resistant forms, patients usually convert to a noninfectious stage in two months, so the patients are kept hospitalized for between four and six months,” notes Keshavjee.

Different Techniques Needed

Lilly also funds other partners to conduct extensive programs in Africa and Asia. Through grants to the International Council of Nurses, the World Medical Association and the International Hospital Federation, integrated TB training programs have been conducted for nurses, doctors and hospital administrators throughout Africa. “The problem with drug-resistant TB in Africa is especially critical,” says Lilly’s Carlevaro. “In Africa, 50 to 60 percent of the patients with HIV die from TB. If they’re not treated, they die very quickly, sometimes within a few weeks,” she explains.

Nonmedical measures are sometimes essential to effective implementation of the partnership, according to Carlevaro. “The Red Cross has more than 100 million volunteers globally, who go house to house, providing incentives such as a kilogram of sugar, for people who need treatment,” she says. “It seems strange because in the developed world, if you’re sick, you are usually willing to get treatment, especially if it’s free. In some parts of the world, however, if you’re sick, you can’t get to the treatment. In some cases if patients take the drugs for a few months, feel better, and then stop, they become re-infected. So, we try to make sure they complete their treatment.” While the course of treatment for regular active tuberculosis takes about six months, for the drug-resistant kind it lasts up to two years,” says Carlevaro.

“The medicines can have a bad side effect profile, with almost universal nausea and vomiting. Patients sometimes don’t have families and social support, and they may lack nutrition, so the Red Cross delivers food assistance and helps patients take their medicines,” says Keshavjee.

Coordination Challenges

The Lilly MDR-TB Partnership is active in close to 80 countries across five continents, and virtually all partners agree that there have been logistical challenges in working in developing countries. When the Green Light Committee has to change its forecasts for drug purchases, the manufacturing partners must adapt their manufacturing schedules. On the other hand, the manufacturing partners also rely on WHO for its quality approvals, and slow response times and policy disagreements have sometimes frustrated partners and those waiting to receive the medicines. Some partners have had difficulty scheduling around grant disbursements and project evaluation requirements.

Prequalification procedures for drug quality and safety measures have taken more time for companies in developing countries to master. Thus, while the supply of drugs to the developing world has been able to meet demand to date, delays in getting one of the Lilly partner's manufacturing facilities approved, have been addressed so that future supply lines will not be affected.

"What Lilly has done with their technology partnership is very innovative," says Keshavjee, who lead-authored a white paper in November 2009 on barriers to solving the problem for the Institute of Medicine last fall entitled: "Stemming the Tide of Multidrug-Resistant Tuberculosis: Major Barriers to Addressing the Growing Epidemic." MDR-TB is very concentrated in southern Africa, India, China and Russia, and Lilly has transferred its technology to companies in each of those regions.

Lilly's technology transfer process has been very complicated. For example, the fermentation process required for capreomycin is a highly challenging and sophisticated process in any country. Hisun Pharmaceutical also had other challenges to address in safety and quality control, and Lilly had to provide support as part of the technology transfer.

In addition, there are sometimes problems with compliance by the manufacturers with the quality approval process in developing countries. "Some manufacturers don't want to go through the WHO process because it takes too long," says Judd. "So, some of the nonquality-approved products may not be good, or we have no way of knowing whether they're good or not." That is why the Lilly partnership has been critical to ensure that their partner manufacturers will go through either the prequalification process or approval by a stringent regulatory authority such as the U.S. Food and Drug Administration or the European Union. Lilly itself doesn't need to go through the process because it is FDA-approved. As an important milestone in the Lilly MDR-TB Partnership, in June 2009, WHO added Lilly manufacturing partner Aspen Pharmacare's cycloserine to its prequalified list.

Other problems of coordination also exist, Keshavjee adds. "We don't know exactly how much medicine countries need," he says. "Say they're going to treat 2,000 patients next year but they don't have the capacity or the labs, and they really end up treating 20 or 100. It's very difficult to forecast what's going to be done. It's a problem with implementation within countries in some cases," he says.

While coordination is a challenge, the partnership has succeeded in multiple spheres in its fight against MDR-TB. Through its multi-pronged approach, it has dramatically increased the supply of essential medicines and enabled manufacturers in high-burden countries to produce these drugs as well. However, the partnership realizes that drugs are not enough, and partner achievements have also been crucial in this battle.

By the Numbers

- The International Council of Nurses has trained nurses worldwide in treating MDR-TB, with an estimated 16,000 nurses trained to date.
- Through programs led by PIH, more than 2,000 people have been trained on TB prevention, hospital management and clinical trainings in Russia and India alone.
- The International Federation of Red Cross held public awareness and antistigma campaigns that have reached more than 15,000 people in Kazakhstan, Romania, South Africa and Uzbekistan.
- Around 2,000 Red Cross Red Crescent staff volunteers have been trained in TB and MDR-TB, and nearly 1,000 community leaders received sensitization training.
- More than 300 clients with TB/MDR-TB signs are referred monthly to TB institutions, while more than 3,000 household visits have been conducted with MDR-TB prevention sessions.
- The International Hospital Federation has disseminated TB and MDR-TB control training manuals to aid hospital managers in more than 40,000 public and private hospitals and clinics in some 100 countries.

The impressive achievements of these partners augment Lilly's effort in fighting MDR-TB by ensuring that the increased supply of MDR-TB drugs are put to proper use through consistent training of medical workers on an international scale. Furthermore, the awareness and advocacy work of the partners reduces stigma and increases awareness, which ultimately ensures that more people seek treatment for this illness.

By John Otrompke, J.D.

Integrating Neglected Tropical Disease Control: Comparing the Experience in Rwanda and Burundi



Lessons Learned:

- *Accurate epidemiologic information is critical. Verify conventional wisdom.*
- *Empower the projects teams to make decisions and implement plans. Efficiencies in their work should be rewarded and give rise to opportunities to further health care initiatives.*
- *Advocacy in support of Neglected Tropical Diseases control must be conducted at all levels of society — from the highest rungs of government to the bottom of the village hierarchy.*
- *The objectives of a national health program and the national health strategy should be aligned.*
- *Ministry of health ownership of NTD control is critical to its long-term viability.*



Doctor palpating to check for worms.

Photo by Lindsay Wheeler, Global Network for Neglected Tropical Diseases

The 13 parasitic and bacterial infections that are considered neglected tropical diseases (NTDs) afflict a billion people, take half a million lives each year and impose a health burden on the world that adds up to a staggering 56.6 million disability adjusted life years. Seven of these diseases are responsible for 90 percent of this devastation. They include (see Table I) lymphatic filariasis (elephantiasis), schistosomiasis (bilharzia), onchocerciasis (river blindness), blinding trachoma (a bacterial infection of the eyes) and the three distinct kinds of worm infestation (trichuriasis, hookworm infections and ascariasis) collectively known as soil transmitted helminthiases (STH). Though each of these seven NTDs can be cured with the use of safe and generally inexpensive drugs, they continue to exact a grim toll on the poorest of the world's poor. Left untreated, the infections compromise the ability of adults to work. They also stunt the physical and intellectual growth of children: Those chronically infected with hookworm grow up to earn 43 percent

less than do their uninfected peers. And so the widespread persistence of NTDs perpetuates a cruel cycle of disease and poverty, hampering the economic advancement of many developing countries.

The densely populated and mountainous East African nations of Rwanda and Burundi are no exception. Both carry a heavy burden of NTDs but, before 2007, neither had comprehensively determined the extent of the problem or devised a strategy to deal with it. To address this need, the global investment firm Legatum — whose interest stemmed from the low cost and high return on investment in NTD control and the opportunity to apply private sector best practices to the effort — contributed \$8.9 million for the establishment of an NTD control program in the two countries. Legatum funneled its support through the philanthropy advisory service Geneva Global, which manages funding to the programs, monitors them and evaluates their progress.

The programs themselves are overseen by the Global Network for Neglected Tropical Diseases, an initiative of the Sabin Vaccine Institute, which, in turn, relies on the Earth Institute at Columbia

University's Access Project in Rwanda and CBM (formerly known as Christian Blind Mission) in Burundi to manage operations on the ground. All of these organizations also work closely with the Schistosomiasis Control Initiative (SCI), which provides technical guidance to the effort (its founder, Alan Fenwick, directs the overall program). But the key partnership of both control programs is that with the Ministry of Health (MoH), with which each works to conduct everything from disease surveillance to mass drug administration (MDA) for the treatment of NTDs.

The control programs both integrate their operations with existing programs for health intervention — namely the Mother and Child Health Week run by the MoH in collaboration with UNICEF. Notably, the program in Burundi had initially sought to work through an army of community drug distributors who had been trained by the African Programme for Onchocerciasis Control (APOC) to distribute drugs against onchocerciasis. The approach, pioneered by APOC, relies on community leaders and other trusted members of society to distribute drugs in MDA campaigns.

But after a pilot round of MDA in three provinces, it quickly became clear that adding further NTD control responsibilities to the already full plates of community drug distributors was neither fair nor practical. So the Burundi program too chose to integrate its operations with those of its existing Mother and Child Health

Week, relying on trained health workers and schoolteachers to carry out the drug distribution. Both control programs have been deliberately structured to build in the health ministry of each country a sense of ownership for NTD control, as well as the technical capacity to sustain it.

This is not easily accomplished. Though lately the darling of international donors, Rwanda continues to lack vital infrastructure and is deeply scarred from the 1994 genocide in which an estimated 800,000 of its citizens lost their lives. Burundi, meanwhile, remains a cauldron of instability. Aside from its own legacy of intertribal conflict and genocide, the country is troubled by recurrent bouts of civil war. Indeed, fighting flared up in April 2008, even as the control program conducted monitoring and evaluation activities. Such instability has, in general, discouraged most donors from investing in the nation's development.

Despite these challenges, the two control programs have conducted several highly effective MDAs. The Burundi program has already delivered about 13 million treatments for STH and more than a million for schistosomiasis over the first two years of its operation. The program in Rwanda, meanwhile, has delivered about 13 million STH treatments and more than 400,000 treatments for schistosomiasis over that period. Notably, over the course of the first year of operation, more than 3.2 million individuals were

Table I: The Major Neglected Tropical Diseases of Rwanda and Burundi

Disease	Causes and Consequences	Chemotherapy
Schistosomiasis (also known as snail fever or bilharzia) 200 million infected worldwide	Caused by a blood-borne fluke that is transmitted via fresh-water snails, schistosomiasis kills more people than any other NTD. A common sign of infestation is blood in urine or stools. Left untreated, it can cause bladder, liver, spleen and kidney damage.	Praziquantel
Soil-transmitted helminthiasis Up to 2 billion infected worldwide	The term for three distinct types of worm infestation — ascariasis, hookworm infection and trichuriasis — STH is associated with poor sanitation and dirty water. Chronic infestation can cause anemia, malnutrition and stunt the physical and intellectual growth of children.	Ivermectin, Albendazole, Mebendazole
Onchocerciasis (river blindness) 37 million infected worldwide	Caused by a parasitic worm transmitted by black flies, this disease is characterized by intense itching, disfiguring skin conditions and eye lesions that can lead to total blindness.	Ivermectin and Albendazole
Trachoma 84 million infected worldwide	This bacterial infection of the eyes, spread by flies and contact with infectious discharge, is the world's leading cause of preventable blindness. As the infection progresses, scar tissue develops on the upper eyelid, turning it inward. Eyelashes scratch the cornea, causing blindness.	Zithromax

Table I information was provided by the Global Network for Neglected Tropical Diseases.



Adults waiting to receive Ivermectin

Photo by Global Network for Neglected Tropical Diseases

treated in Burundi and Rwanda combined at a cost per person of approximately 51 cents (second-year calculations have not yet been completed). Today the programs have only one outstanding item to address on their NTD agenda: trachoma. Having established that it is endemic in Burundi, though not in Rwanda, they are currently applying to the International Trachoma Initiative for the antibiotics required for treating the disease via MDAs in Burundi and as required in Rwanda.

This case study examines how the two control programs evolved from their planning stages through to the second year of their operation. It focuses, in particular, on key aspects of the partnerships — between government and global health agencies, nongovernmental organizations (NGOs) and local communities — that have had a significant impact on the efficiency of the enterprise.

Starting Up

The biggest challenge both programs faced at the outset was that there was scant information about the distribution of tropical diseases in Rwanda and Burundi. To fill in that critical gap, each control program began in mid-2007 to gather data for a national map of NTDs, an effort that was integrated in Burundi, though not in Rwanda. Prior to their arrival on the scene, onchocerciasis was the only such disease to have been mapped across the region.

It had been found to be absent in Rwanda, but not Burundi, where it was the focus of a collaboration between the government's Programme National de Lutte contre l'Onchocercose (PNLO) and APOC.

The mapping effort in Rwanda was complicated by the fact that the Ministry of Education did not know where all of the nation's schools are located, and surveys of schoolchildren are vital to the accurate mapping of schistosomiasis and STH. As a consequence, the mapping effort in that country also became something of a census of Rwanda's educational system. The ministry now has a complete map of the nation's schools.

The control programs' maps revealed that the only major NTD that isn't an issue in either of the countries, due primarily to their elevation, is lymphatic filariasis. STH, on the other hand, is widespread in both, affecting as many as four in 10 people across Burundi, and 65 percent of schoolchildren in Rwanda, with the prevalence reaching 90 percent in some areas in that country. Schistosomiasis, meanwhile, was found to be entrenched around major bodies of water in both Rwanda and Burundi. Finally, trachoma — which has long been believed not to be a problem in either country — turned out to be highly prevalent in Burundi.

The two programs also began from the outset in 2007 to address the shortage of human resources for NTD control. In Burundi, the MoH worked closely with CBM and SCI to train all control program staff in the diagnosis and treatment of the major NTDs. Staff in both countries were trained in data management and analysis as well, building an eminently transferrable set of vital technical skills. Beyond that, the program in Burundi saw to the training of more than 11,000 community health workers, teachers and community drug distributors in the treatment of the targeted NTDs. Similarly, the Access Project in Rwanda collaborated with the Treatment and Research Center for AIDS and other Pandemics (TRAC+), a program of the MoH, to train more than 10,000 community health workers, teachers, lab technicians and other national health care staff. The World Health Organization also contributed to the effort, conducting the training of nearly 100

health care workers and control program staff members in NTD assessment and diagnosis in both countries.

Ministries Matter

Since a nationwide project targeting onchocerciasis was already under way in Burundi, the control program did not include the disease in its efforts. It did, however, incorporate its operations with those of the Mother and Child Health Week. This not only cut costs — through the pooling of resources — but helped the control program to learn from and build off the systems already put in place. But what truly distinguished Burundi's program from that of Rwanda's, especially in the early stages, was the involvement and enthusiasm of its MoH.

Although beset by troubles ranging from fuel shortages to striking doctors, the NTD control program in Burundi remained squarely in the focus of the MoH. Key to this success was the establishment of a leadership team in the ministry dedicated to the effort. It kept the program running despite three changes in leadership of the department in the span of just two years. The ministry's commitment was also evident in its willingness to invest precious resources to the control program; it shared office space and provided its own vehicles, nurses and technicians to support the effort.

This not only affected the bottom line — only eight percent of the Burundi control program's total expenditures in the first year, for example, were for personnel costs. It also served to root the initiative firmly in the MoH, which has since assumed an unequivocal leadership role. "Ministry leadership may mean the program is slower, less efficient and prone to internal conflicts," says SCI Director Alan Fenwick. "But it also means that, in the long term, the ownership of the control program for tropical diseases belongs to the Burundians and their Ministry of Health."

By contrast, the Rwandan MoH took only a tepid interest in the control program when it was launched in mid-2007. It appeared reluctant at the outset to invest much of its limited human and material resources in the effort, and the Access Project had to compile its NTD team almost from scratch. As a consequence, 39 percent of the Rwandan control program's expenditures in the first year were for staffing.

In an effort to get the MoH more deeply involved, the Access Project — which renamed itself the NTD/Access Project — established with ministry staff a joint task force to sensitize people across Rwanda's health system on NTDs and, in some cases, to train them in diagnosis and treatment of the diseases. Further, the task force submitted to the ministry a strategic plan for integrating NTD control into its TRAC+ initiative.



Felix in Kirundo infected with schistosomiasis

Photo by Lindsay Wheeler

These steps were critical. They account, at least in part, for the increased ministry involvement in the second year of the program. Indeed, in August 2008, the Access Project pooled resources with TRAC+ to deworm some 3.8 million children and expectant mothers during the annual Mother and Child Health Week overseen by the MoH. “We’re seeing the beginnings of an integrated health platform within Rwanda’s districts,” says Kari Stoever, managing director of the Global Network. “That’s exactly what we want to see from the perspective of sustainability.”

But why, in the first place, was the Rwandan ministry so much slower to respond than the one in Burundi? This probably had something to do with its absorption in efforts to combat AIDS, tuberculosis and malaria — the three major epidemics of the region, says Fenwick. But it also had to do with the lack of data about the prevalence of NTDs in the country: the Rwandan MoH simply didn’t think there was a big enough NTD problem in its jurisdiction to warrant concerted action. After its leaders saw the maps of NTD distribution, says the Access Project’s Denise Mupfasoni, the NTD control program’s Rwanda national coordinator, the ministry was quick to take on a more active role.

But another factor contributed to ministry’s initial reluctance: Unlike its Burundian counterpart, the Rwandan ministry lacked clear policy guidance on NTD control. One of the four prime objectives of Burundi’s health development plan, after all, is to “reduce the prevalence of transmittable and nontransmittable diseases,” such as NTDs. “The crucial thing to remember about any NTD program,” says Fenwick, “is that it cannot happen without external impetus. So we needed to do our advocacy at all levels. We needed to convince the Ministry of Health of our target countries to write specifically in their strategic plans: ‘We will control neglected tropical diseases and improve child health through deworming.’”

Once senior government officials are made aware of the severity of the problem and the low cost and relative ease of dealing with a number of tropical diseases, says Fenwick, they are only too happy to cooperate. And their support is invaluable, as it sends a powerful signal of endorsement down the rungs of the national bureaucracy that can be critical to garnering support for ground operations from local officials.

Getting buy-in from the target population is another matter. It certainly helped that each of the control programs had access to existing national health care initiatives to reach as many people as possible. The Rwanda program operated via TRAC+ and a joint program of the MoH and UNICEF — called Mother and Child Health Week — that delivered bed nets, vaccinations and nutrients to mothers and young children. The Burundi control program’s

MDAs too were integrated into an almost identical program run by its MoH and UNICEF.

All this brought people to the table. But getting them to take drugs for parasitic diseases required a more concerted effort. The rural populations of both countries have been disease-ridden for so long that many people do not even consider infection with NTDs to be preventable or, indeed, anything out of the ordinary. To get such people to participate in the MDA, the control programs invested generously in national media campaigns in both countries when they launched their second major MDA campaigns in the latter half of 2008. Thousands of posters, booklets and leaflets about NTD prevention were directed not only at communities but used to educate health workers and the staff of a variety of NGOs as well. Mupfasoni suspects that without that campaign — especially the radio messages, which had the greatest reach — most people would have refused to take drugs in the absence of symptoms. As it turned out, the MDA covered an estimated 80 percent of the target population in Rwanda and 91 percent of the population of Burundi.

Best Business Practices

From the project management perspective, says Stoever, the greatest successes of both control programs was not just the efficiencies they achieved — both came in well under budget in the first year of operation — but how those efficiencies were leveraged. When project teams find they are coming in under budget, she explains, they often tend to panic, assuming that they will either be penalized for overbudgeting or lose the money that they saved by dint of shrewd planning and execution. As a consequence, there’s a high incentive to spend such extra funds in almost any justifiable fashion.

This was something Stoever wanted to avoid. “We wanted to be flexible and create an environment of partnership that would reassure them that we would not be penalizing efficiencies,” she says. After all, the donor organization Legatum had expressed a particular interest in whether best business practices could be applied to the NTD control programs it was underwriting.

Rewarding efficiency and initiative certainly qualified. So when the joint program teams asked how they ought to spend their excess money, she first reassured them that they would not lose their funds. She then suggested they take a little time to mull over how the money might be redirected in service of the ultimate objectives of the control program — the elimination of the major NTDs.

The two programs returned with different prescriptions. The Burundi team believed that the money it had saved would be best spent to buy an extra couple of rounds of MDA, extending their program by a year. The Rwanda team, on the other hand, felt that



Children in Burundi

Photo by Lindsay Wheeler, Global Network for Neglected Tropical Diseases

the dire shortage of potable water and basic sanitation systems across rural areas were severely compromising NTD control. It wanted to use the spare funds to supplement existing projects to shore up such infrastructure, particularly in schools located in high-endemic areas. “By being open with them,” says Stoeber, “we were able to be more creative, more innovative and more efficient. When they realized they would not be penalized for underspending, we could open the dialogue with them about what other things we could achieve with those resources. That’s an innovative approach to partnership.”

The Way Forward

Still, there remains room for improvement in the processes that made such savings possible. Although organizationally integrated in the ministries of health, says Fenwick, neither the Rwanda nor the Burundi control programs have figured out yet how best to integrate the delivery of different drugs in one visit. This is in part due to the distribution of the diseases in both countries — people with STH may or may not have schistosomiasis, especially in areas distant from major bodies of water.

This raises another problem, evident in the pilot phase of the Burundi program: the burden placed on community drug distributors who are asked to deliver drugs for multiple diseases at

different times. Since these volunteers are critical to the efficiencies associated with a community-directed approach to MDA, their concerns must be taken into account in any program. Indeed, the Burundi program had to stop working with the drug distributors trained by APOC/PNLO due to the extraordinary demands this imposed on their time. It was fortunate to be able to integrate its operations with those of another national health program, which had its own cadre of drug distributors. Since the Mother and Child Health Week is an initiative active in other countries as well, it could be harnessed to distribute NTD treatments should those nations wish to implement similar programs.

Today, both control programs are monitoring their impact on NTD prevalence to fine-tune strategies. But the shortage of adequate infrastructure remains a major challenge to the sustainability of NTD control. Parasitic diseases — notably ascariasis — often return to their original levels relatively swiftly after the completion of MDAs, observes Mupfasoni. Any lasting solution to the NTD problem in both countries will inevitably depend on better sanitation and the widespread installation of infrastructure for clean water.

By Unmesh Kher

Integrating Neglected Tropical Disease Control: Common Themes in Niger and Zanzibar



Lessons Learned:

- *Early engagement and active support by political leaders aids in neglected tropical disease control efforts.*
- *Community mobilization hinges on buy-in from community leaders, religious figures and local politicians.*
- *Make sure that health care workers at every level of the health system have bought into the program and are made explicitly aware of its high priority.*
- *Mass drug administration must be coupled with effective health education and other measures to ensure adequate long-term adoption and prevent further disease transmission.*



Photo by Shutterstock® Images

Neglected tropical diseases (NTDs) are a set of 13 parasitic and bacterial infections that affect more than a billion people worldwide and take a half million lives each year. Yet, like so many diseases that afflict the poorest of the poor, many of them are not adequately addressed by health agencies today, even though most are eminently preventable and relatively easily treated. This makes NTDs ideal candidates for national disease control programs. And, over the past decade, a number of such efforts supported by donors and drug companies have been launched by government agencies in collaboration with international nongovernmental organizations. These programs have sought mainly to control or eliminate one or more of seven major NTDs (See Table I): lymphatic filariasis (elephantiasis), schistosomiasis (bilharzia), onchocerciasis (river blindness), blinding trachoma (a bacterial infection of the eyes) and the worm infestations — ascariasis, trichuriasis and hookworm — collectively known as soil transmitted helminthiasis (STH).

Many of these programs first started conducting mass drug administration (MDA) campaigns against individual tropical diseases in Africa in the early years of this decade. To do so, they often employ an approach that relies on volunteer drug distributors who have been identified by their social peers as trusted members of the community. The volunteers are trained by health workers and partnering organizations to distribute the right drugs in the right dosages to the right people and are then mobilized during mass treatment campaigns. Such community-directed interventions have been shown empirically to be far more effective in reaching people during an MDA than traditional modes of drug distribution.

As the control programs using these sorts of approaches (see Table IIa and IIb) expanded their geographic coverage, they soon realized that they were often trying to reach the same people in Africa; many of the tropical diseases are endemic in the same areas, and coinfection with NTDs is not uncommon. It was obvious that combining basic operations, such as disease surveillance, drug delivery and the training of volunteers and health workers in MDA and diagnostics, would do much to boost the cost efficiencies of the overall effort. With the encouragement of the World Health Organization (WHO) and the Bill & Melinda Gates Foundation, which funds many of these efforts, the various control initiatives

thus began in 2006 to work closely with each other and with national health agencies to integrate their operations.

This case study examines how that process unfolded in Zanzibar and Niger. It explores, in particular, practices in the management of partnerships and personnel that are likely to be critical to any future integrated, community-directed MDA campaign against diseases of the developing world.

The Arenas

A semi-autonomous territory of Tanzania, Zanzibar is an archipelago of several small islands and two large ones, Unguja and Pemba, which have a combined population of 1.2 million. Niger, on the other hand, is a vast, landlocked country in Western Africa whose Northern and Eastern regions lie under the Sahara Desert. As a consequence, most of its 14 million, largely impoverished citizens live in the South and West of the country, concentrated in the Niger River basin, where subsistence agriculture is at least possible.

Though the two countries could not in demographic, cultural and geographic terms be more different, they do share some similarities. Zanzibar, like Niger, is largely peopled by the rural poor. Both

countries are also short on basic infrastructure for clean water and sanitation. As might be expected, schistosomiasis, lymphatic filariasis (LF) and the STHs, which all thrive in conditions of poor hygiene and poverty, have historically been rampant in both regions. Blinding trachoma, a bacterial infection typically found in dry areas, is not a problem in Zanzibar, but is widespread in Niger.

The Campaign in Zanzibar

Although Zanzibar has been the focus of efforts to control parasitic diseases for roughly two decades, the first of the control programs relevant to this case study started only in 2001. That was when the Global Alliance to Eliminate Lymphatic Filariasis and the Zanzibar Ministry of Health and Social Welfare launched an annual community-directed MDA program to eliminate LF on both islands using drugs donated by Merck & Co. and GlaxoSmithKline. If taken just once a year over a five-year period, those drugs — Mectizan (ivermectin) and albendazole — eliminate not only the parasites responsible for LF, but intestinal worms as well.

Two years later, the Gates Foundation-funded Schistosomiasis Control Initiative (SCI) and a team from the British Natural History Museum funded by UK's Health Foundation, began working with

Table I: The Major NTDs of Niger and Zanzibar

Disease	Causes and Consequences	Chemotherapy
Schistosomiasis (snail fever, bilharzia) 200 million infected worldwide	Caused by a blood-borne fluke that is transmitted via fresh-water snails, schistosomiasis kills more people than any other NTD. A common sign of infestation is blood in urine or stools. Left untreated, it can cause bladder, liver, spleen and kidney damage.	Praziquantel
Soil-transmitted helminthiasis Up to 2 billion infected worldwide	The term for three distinct types of worm infection — ascariasis, hookworm infection and trichuriasis — STHs are associated with poor sanitation and dirty water. Chronic infestation can cause anemia, malnutrition and stunt the physical and intellectual growth of children.	Ivermectin, Albendazole, Mebendazole
Onchocerciasis (river blindness) 37 million infected worldwide (Not prevalent in Zanzibar and almost eliminated in Niger)	Caused by a parasitic worm transmitted by black flies, this disease is characterized by intense itching, disfiguring skin conditions and eye lesions that can lead to total blindness.	Ivermectin
Lymphatic filariasis (elephantiasis) 120 million infected worldwide	A parasitic worm transmitted by mosquitoes causes this disease. The larvae of the parasites circulate in the skin, causing intense itching, while the adult worms severely damage the lymphatic system. Victims suffer from severe disfiguration and incapacitation due to swollen limbs and thickened skin.	Ivermectin and Albendazole
Trachoma 84 million infected worldwide (Not prevalent in Zanzibar)	This bacterial infection of the eyes, spread by flies and contact with infectious discharge, is the world's leading cause of preventable blindness. As the infection progresses, scar tissue develops on the upper eyelid, turning it inward. Eyelashes scratch the cornea, causing blindness.	Zithromax

Table I information was provided by the Global Network for Neglected Tropical Diseases.

the ministry on a separate program to bring STH and schistosomiasis under control on the islands. Named the “Kick out Kichocho” program, it involved annual combined MDAs of albendazole with praziquantel, the medicine for treating schistosomiasis. The treatments were aimed at school-aged children on Unguja, and at both adults and children at risk for infection on the island of Pemba. This partnership culminated in late 2006 with the integration of the schistosomiasis control program and the LF elimination program. (For a full listing of partners involved in Niger’s and Zanzibar’s NTD control programs, see Tables IIa and IIb.)

Piggybacking on the systems and human resources already established by the LF initiative, the integrated program first conducted a pilot study. Drugs against all three of the NTDs were administered at the same time to 5,500 people in high-risk areas. When it was clear that there were no adverse events from the triple therapy, the entire eligible population of Zanzibar — totaling some 700,000 people — was treated with the three drugs. The integrated program established for the first time that, in places where the prevalence of the targeted NTDs has been reduced substantially, such triple drug therapy can be given safely to people who have had extensive exposure to the drug therapies employed. The MDAs over the past several years have, further, had the combined effect of virtually eliminating LF from the islands and significantly reducing both the prevalence and the intensity of schistosomiasis and STH.

But, notably, the last two diseases persist in hotspots of infection on the islands.

The Campaign in Niger

Niger was in a very different place when it chose to integrate its NTD control programs. A highly effective campaign had already succeeded in eliminating river blindness in the country. But other control efforts had begun in earnest there only in 2003, when the Ministry of Health (MoH) and the International Trachoma Initiative launched a program for trachoma focused on the dry, eastern part of the country. Next, schistosomiasis and STH were targeted by an MoH treatment program that began in 2004 in partnership with SCI. By 2007 the schistosomiasis and STH program had reached approximately 6.2 million people through annual MDAs. The control of LF, on the other hand, had never quite progressed beyond its planning stages.

In 2007, Niger’s MoH, with funding from the United States Agency for International Development (USAID) supported by additional funds from the Bill & Melinda Gates Foundation, set about integrating its independent NTD control efforts, adding a program for LF elimination to the mix. Because Nigeriens had not had quite as much exposure to the drugs used to treat these diseases, triple drug therapy was not considered. But other aspects of the community-directed MDA were amenable to integration.

Table IIa: Niger

Organization	Role
Ministry of Health	Coordinated the integrated NTD control program in Niger
USAID/RTI International	USAID funded the effort through its NTD control program, which is managed by RTI International. Niger was one of the first five fast-track countries selected by USAID to receive funding for MDAs against the major NTDs.
Schistosomiasis Control Initiative at Imperial College London	SCI was established in 2002 with a grant from the Bill & Melinda Gates Foundation to oversee programs for schistosomiasis and soil-transmitted helminth control. SCI worked with Niger’s Ministry of Health and Ministry of Education, providing funding and expert advice to the nation’s disease control program.
International Trachoma Initiative	ITI was founded by Pfizer Inc. and the Edna McConnell Clark Foundation in 1998 in response to the WHO’s call to eliminate blinding trachoma by the year 2020. It collaborates with governments and NGOs to implement the SAFE strategy for trachoma elimination. ITI has been working in Niger since 2001.
Global Alliance to Eliminate Lymphatic Filariasis	Established in 2000, GAELF is a public-private partnership involved in advocacy, resource mobilization and program implementation for lymphatic filariasis control. GlaxoSmithKline and Merck & Co. have pledged the albendazole and Mectizan (Ivermectin) necessary to achieve elimination of lymphatic filariasis. Valued at more than \$1 billion, these are the largest drug donations in history.
World Health Organization	The WHO is the overall coordinating health authority within the United Nations and is responsible for providing guidance to ministries of health. Its NTD department was established in 2006.
RISEAL	A nonprofit multi-disciplinary association of scientists and technicians that provides technical advice to developing countries in West Africa on a variety of disease control issues.

This included the diagnosis of NTDs and the prevalence mapping that is essential to both an effective MDA and its evaluation. It also included the delivery of drugs, the training of trainers who would teach volunteers how to administer those drugs and the actual training of those volunteers. Some aspects of disease control, however, could not be integrated — most notably the eye surgeries for trachoma and the hydrocele surgeries for LF. In all, some 18,000 people were trained in 2007, mainly as drug distributors. The first integrated, community-directed drug delivery, using drugs donated by Pfizer Inc., Merck & Co., GlaxoSmithKline and UNICEF, reached 5.2 million people in 19 districts of Niger in 2007, and approximately eight million in 26 districts in 2008.

Harnessing Political Support

If any single thing accounted for the relatively smooth integration of independent control programs in Zanzibar and Niger, it was the strong and clear backing each enjoyed from

the government. That support was, in fact, assiduously cultivated by SCI Director Alan Fenwick and other project leaders well before either of the programs started. “We have gone up the political hierarchy in both countries,” says Fenwick, “and made sure that we have buy-in at the highest levels — and that this buy-in is replicated at every level in the chain of command.”

As a consequence of this high-level advocacy, the presidents and ministers of health of both Zanzibar and Niger participated in the televised launch of their NTD control programs. The signal of political support is of critical importance, says Fenwick. A phone call from high up the chain of command can do much to end turf wars and other conflicts that could interfere with swift decision-making or otherwise hamper the MDA.

Managing the Integration

But not all problems are best resolved through such channels. In Niger, for example, news of integration initially caused some consternation in the Ministry of Health. Many within the ministry who were working on independent control programs against trachoma, schistosomiasis or LF feared that they would lose their jobs with program integration. That concern, at least, was relatively easily resolved. “The main thing we had to convey was that we weren’t thinking that one person would now be doing three people’s jobs

in the ministry,” says Fenwick. “In fact, there would be more to do because by rationalizing the work and bringing in more funding we were able to expand the coverage of the control programs.”

Turf too was an issue. Dr. Amadou Garba, who oversees Niger’s NTD control efforts, recalls that such interdepartmental tussles were addressed by reminding the vertical program managers that they would be better able to loosen government purse strings and mobilize resources if they pulled together. “They recognized that, working together, we would be much stronger in our advocacy for mobilizing the resources of the department,” says Garba. Beyond that, everyone was aware that the USAID support was intended for an integrated MDA program, so collaboration was required for funding.

The managers of individual control programs had some concerns about strategy as well. The trachoma team worried, for example, that with all the focus on MDA, vital elements of its own approach to disease control would be neglected. Its particular concern was that the WHO-recommended strategy for trachoma elimination would get short shrift. The SAFE strategy, as it is known, includes treatment with antibiotics. But it also encompasses eyelid surgeries to improve vision and the promotion of facial cleanliness and environmental improvements to minimize transmission.

Table IIb: Zanzibar

Organization	Role
Ministry of Health and Social Welfare	Members of the helminth control teams at the ministry have been directly involved with implementation of Zanzibar’s integrated NTD program.
Schistosomiasis Control Initiative at Imperial College London	SCI was established in 2002 with a grant from the Bill & Melinda Gates Foundation to oversee programs for schistosomiasis and soil-transmitted helminth control. SCI worked with Zanzibar’s Ministry of Health and Social Welfare, providing funding and expert advice to the nation’s NTD control program.
Health Foundation	An independent charity dedicated to improving health care worldwide, HF helped to fund schistosomiasis control on the islands.
Natural History Museum	The Wolfson Wellcome Biomedical Laboratories at the Natural History Museum have a research interest in NTDs, particularly schistosomiasis. Its early work in Zanzibar led to the “Kick Out Kichocho” program.
Liverpool School of Tropical Medicine	This medical college houses the nonprofit Lymphatic Filariasis Support Centre, which serves as the Secretariat for the Global Alliance for Elimination of Lymphatic Filariasis (GAELF)
Global Alliance to Eliminate Lymphatic Filariasis	Established in 2000, GAELF is a public-private partnership involved in all aspects of lymphatic filariasis control. GlaxoSmithKline and Merck & Co. have pledged all the albendazole and Mectizan (Ivermectin) necessary for elimination of lymphatic filariasis. Valued at more than \$1 billion, these are the largest drug donations in history.
World Health Organization	The WHO is the overall coordinating health authority within the United Nations and is responsible for providing guidance to ministries of health. Its NTD Department was established in 2006.
Ivo de Carneri Foundation	The foundation, in collaboration with the health ministry, runs a public health research laboratory on Pemba Island, which was the focal point for SCI’s monitoring and evaluation activities.
EU Framework 6-CONTRAST	A European Union funded project, CONTRAST is investigating in Zanzibar the role of community-led programs for NTD control.

To address this concern, says Garba, program managers acknowledged that all of the diseases being targeted arise in some measure from contaminated water and poor hygiene. “We worked together,” he says, “to elaborate some messages on hygiene and water supply and integrate them into the program.” Not surprisingly, Niger’s NTD control program today also covers, in collaboration with the vertical control programs, the delivery of surgeries to address the morbidity associated with trachoma and LF. That is not a feature of national NTD control plans that always gets implemented, according to Elisa Bosqué-Oliva, who was SCI’s program manager for Niger.

The managers within the ministry were not the only people whose support was deemed critical to successful integration. In both Niger and Zanzibar, stakeholder meetings

organized from the start of the process brought all parties together and gave them opportunities to air their concerns, explain what they brought to the table and what they were willing and able to contribute to the integrated program. “Integration, in my mind,” says Fenwick, “is communication, collaboration and cooperation.”

That cooperation is of particular importance at the district level. Health workers at this level are essential to the planning and execution of MDAs, since they know most about the local conditions. That includes such things as the actual population in their area, where the schools are located and how many vehicles, educational pamphlets and other resources might be required to cover the region. But because the integrated MDA program is run by a government ministry, says Bosqué-Oliva, health workers are only paid the government per diem, which is lower than that of some other health initiatives active in Niger. This can understandably influence how regional workers manage their time, often to the detriment of ministry-run programs. High-level endorsement — including letters sent out by senior officials of the Ministry of Health requesting that the integrated MDA be given top priority — prevented the program from becoming a second-tier operation for these workers.

Engaging Community Leaders

Community leaders and local politicians are another repository of important information, and their active participation is vital to the successful execution of community-directed MDAs. Khalfan Mohammed, who managed Zanzibar’s integrated NTD control campaign, recalls that, when the Ministry of Health and Social Welfare conducted its first MDA for LF in 2001, people in certain pockets of the islands did not turn up to take their medicines. It turned out that many of the stragglers in these areas supported the opposition, and the NTD control program had neglected to consult opposition leaders in the selection of drug distributors. The distributors were, as a consequence, not well-known or trusted in these areas. Coverage, says Mohammed, became far more uniform when the program reached out to leaders across the political spectrum before conducting the next round of MDA.

Understandably, when Zanzibar launched its integrated program five years later it gave high priority to consultations with a variety of local opinion leaders. This ground-level advocacy was reinforced with a large media campaign publicizing the effort. “There was a national sense of ownership for the program that motivated people,” says Mohammed. “The social mobilization component played a key role in that.”

Similarly, in Niger, grassroots leaders and authority figures like imams and respected schoolteachers were tapped for their insights and local knowledge. Their recommendations were taken for the selection of voluntary drug distributors. Garba points out that, without the support of such leaders, control programs distributing drugs donated by Western countries can arouse deep suspicions — not least the notion that the medicines are in fact birth control pills (Niger has both the highest infant mortality rate and the highest birth rate in the world) or vehicles of HIV infection.

Given the intricate web of relationships that supported the two programs, and all that could have gone wrong in their efforts, the community-directed MDAs unfolded remarkably smoothly. They weren’t, however, without their weaknesses. For example, although the prevalence of both schistosomiasis and STH was cut drastically after the MDA in Zanzibar, both diseases later surged in known hotspots on the islands in the absence of annual treatment. This suggests that any future program that seeks to eliminate, and not just control, the targeted NTDs will need to pay special attention to health education, snail control and the construction of infrastructure for basic sanitation and water purification. Similar challenges face the ongoing NTD control program in Niger, where the integrated MDAs have already reached about 60 percent of the population, and the Ministry of Health expects to accomplish more or less full coverage of the country in 2009, and then continue this annually for several years.

If such gains are to be sustained, partnerships central to NTD control in both countries will also need to be expanded. In Zanzibar, the Ministry of Education will have to step up its involvement in NTD control as schoolchildren become the main targets of treatment. In Niger, the Ministry of Health has already assumed that role, but other ministries too must now become involved. These agencies, with their knowledge of where water and agricultural projects are planned, could provide valuable advance notice about the risk of disease outbreaks in various parts of the country. Such information will doubtless play a critical role in protecting hard-won public health gains once the mass community-directed drug administration and other measures have lowered NTD prevalence to manageable levels.

By Unmesh Kher

Human Hookworm Vaccine Initiative Designs Rapid Deployment Strategy for Developing World



Lessons Learned:

- *Strong but flexible program management that coordinates activities, timelines and budgets across continents is critical to achieving success.*
- *Technical challenges can be overcome with a flexible strategy that allows for collaborative approaches by the program's partners.*
- *Functional working relationships with oversight agencies and continued open communication can help partners meet important project milestones.*



Two scientists working at the Belo lab in Brazil.

A global public-private partnership is in the final stages of a product development and technology transfer program that intends to deliver the world's first safe, affordable and effective hookworm vaccine to a neglected population — an estimated 3.2 billion men, women and children who live in impoverished rural areas of sub-Saharan African, Southeast Asia, India and the tropical regions of the Americas and are at risk for hookworm infection.

At the heart of this global access endeavor is the Human Hookworm Vaccine Initiative (HHVI), founded by Peter Hotez, M.D., Ph.D., president of the Sabin Vaccine Institute and distinguished research professor and chair of the Department of Microbiology, Immunology and Tropical Medicine at The George Washington University. The HHVI is a unique nonprofit product development partnership with The George Washington University and based at the Sabin Vaccine Institute in Washington, D.C., with support from the Bill & Melinda Gates Foundation. For close to 10 years this international network of university and government

partners has built the infrastructure, capacity and the operational expertise for research, product development, scale-up and technology transfer of multiple candidate vaccine antigens.

The result of their collaborative activities is the successful manufacture under current good manufacturing practices (cGMP) of two recombinant vaccine antigen candidates and the completion of two Phase I clinical trials in the United States and Brazil, under the oversight of U.S. and Brazilian regulatory and ethical review bodies. The HHVI also has inaugurated a Vaccine Testing Center that includes a clinic and field laboratory in the state of Minas Gerais, Brazil, the site of HHVI clinical testing activities, and embarked on the transfer of product development process to Instituto Butantan, a public-sector vaccine manufacturer in Sao Paulo, which produces 80 percent of the vaccines used in Brazil.

Along the way, the HHVI has overcome challenges and learned lessons in developing a vaccine for global access in the nonprofit sector, specifically as they relate to product design, development and manufacture, introduction and distribution, financing, knowledge dissemination, and intellectual property management.

The HHVI, with its comprehensive approach to vaccine development, is developing a global access roadmap for neglected tropical diseases such as human hookworm — a guide that continues to identify key operational and technical aspects that are essential for a successful partnership with a developing country vaccine manufacturer.

Hookworms: A Global Plague Affecting Billions

Human hookworm infection is a parasitic infection that causes intestinal blood loss leading to iron-deficiency anemia and protein malnutrition, particularly in pregnant women and children. This disease is widespread in tropical and subtropical countries where people may defecate on the ground and where the soil moisture is most favorable for hookworm eggs to develop into larvae (immature worms).

The World Health Organization (WHO) estimates hookworm disease affects 576 million people worldwide. Once a big problem in the Southeastern United States, hookworm disease is now largely controlled in that country. Today, most of the people at risk live in impoverished rural areas of sub-Saharan Africa, Southeast Asia, India and the tropical regions of the Americas.

Hookworm is transmitted via contact with infective third-stage larvae that penetrate through the skin, frequently entering through the hands, feet, arms or legs. Infective third-stage larvae also can be ingested where they migrate to the lungs, are expelled by cough and swallowed into the intestine to become adults. Adult hookworm parasites attach to the small intestine and cause intestinal blood loss, often sufficient to cause anemia and malnutrition. In children, the WHO reports that chronic hookworm infection impairs physical and intellectual development, reduces school performance and attendance, and adversely affects future productivity and wage-earning potential.



Canine hookworm

Today, hookworm infection is controlled with deworming drugs that have high rates of failure, re-infectivity and potential drug resistance. However, there is evidence that a safe and cost-effective vaccine could provide an important new tool for the control of human hookworm infection.

HHVI: A Global Public-Private Partnership with a Mission

As a nonprofit private development (PD) public-private partnership (PPP), the HHVI is achieving successes in its development of a recombinant vaccine for human hookworm infection by engaging a network of collaborative partners with complementary strengths under the guidance of Hotez, its director. With institutions in North and South America, Europe, Asia and Australia, the HHVI has devised a virtual interactive framework with strong program management that coordinates activities, timelines and budgets.

“Unlike the traditional PD-PPP with a reliance on outside contractors, the HHVI also has built an in-house capacity for antigen discovery, preclinical testing, technology transfer and clinical development within its network of nonprofit entities, academic institutions and governmental organizations,” says Ami Shah Brown, Ph.D., M.P.H., director, vaccine operations for the HHVI, who jointly coordinates activities and timelines for the technology transfer program with Maria Elena Bottazzi, Ph.D., director, product development, HHVI.

The HHVI’s existing partnerships are based on longstanding, established academic collaborations between The George Washington University in the United States, the Oswaldo Cruz Foundation in Brazil, London School of Hygiene and Tropical Medicine in England, Institute of Parasitic Diseases in China and Queensland Institute of Medical Research in Australia. The largely academic structure morphed from an academic program to a vaccine development program when the Sabin Vaccine Institute became involved in 2000. Instituto Butantan was the most recent addition to the partnership as plans for technology transfer and global access evolved.

“We’ve adopted this strategy to see whether we can shorten the time between bench discovery and the point where a promising vaccine candidate can be tested in the clinic,” adds Brown.

To date, successes realized by the HHVI in its mission to reduce human suffering from hookworm can be attributed to the strengths and capabilities each member brings to the partnership, as well as the choice of Brazil for manufacturing and clinical testing.

“Brazil is an innovative developing country, a middle-income country with a modest economic capacity but a high capacity to develop, patent, manufacture, ensure safety, market new health

products and to develop, test and introduce new health policies that support products,” says Bottazzi. “Also, there are a large number of people living in certain areas of Brazil who suffer from hookworm infection.”

Management and Administration

- Sabin Vaccine Institute — Chartered as a nonprofit organization to reduce human suffering from infectious and neglected tropical diseases by providing greater access to vaccines and essential medicines through programs of vaccine research, development and advocacy, Sabin provides management, regulatory affairs and quality assurance activities for the HHVI collaborators.

Discovery and Testing

- The George Washington University — Staff in this Washington, D.C., university’s Department of Microbiology, Immunology and Tropical Medicine develops processes for the expression, manufacture, scale-up, formulation and testing of the hookworm vaccine candidates. These processes are designed to maximize manufacturing yields and minimize costs, both essential elements for a product intended for the world’s poor.
- Queensland Institute of Medical Research — This university team, based in Brisbane, Australia, performs research and development activities primarily for candidate antigen early evaluation, characterization and ranking. Staff pursues and evaluates alternative methods to challenges encountered during antigen discovery and early feasibility of expression, which generate and maintain supporting data for the pipeline of candidate antigens.
- Institute of Parasitic Diseases — Located in Shanghai and part of the Chinese government’s Center for Disease Control and Prevention, its staff conducts preclinical testing.

Modeling and Analysis

- London School of Hygiene and Tropical Medicine — Part of the University of London, Britain’s national school of public health provides the HHVI with needed statistical and epidemiologic models and cost-effectiveness analysis for vaccine introduction, distribution and financing — data that are imperative to estimate the global health impact that a hookworm vaccine could have.

Manufacturing and Testing

- Oswaldo Cruz Foundation (FIOCRUZ) — Under a collaborative agreement with the HHVI, this science and technology health institution, which is attached to the Brazilian Ministry of Health, provides the epidemiological assessment, as well as the clinical testing and development of the hookworm vaccine.

- Instituto Butantan — A public-sector vaccine manufacturer under agreement with the HHVI, this biomedical research center affiliated with the São Paulo state secretary of health is involved in technology transfer, scale-up process development and clinical grade manufacture of the hookworm vaccine. It provides qualified cGMP facilities, experienced staff and a history of successful collaborations.

HHVI’s Challenges and Lessons Learned

Since January 2000, when Sabin’s Vaccine Development Program launched the HHVI, challenges have surfaced: programmatic transitions, financial resources and risk management, as well as geographic distance, time zones, and differences in culture and language. But the program has and continues to overcome them with a flexible and committed approach to continuous communication, strong technical capacity and infrastructure, quality management, respect for autonomy, and transparency in decision-making. Its successes are based on a fundamental belief in strong partnerships and collaborations, shared intellectual property and ownership of discoveries, and a management framework coupled with careful technical planning.

The Sabin Vaccine Institute management team learned that strong operational, regulatory and quality-assurance management based on expertise, open and regular communication between partners and well-planned and documented strategies are essential components for a successful vaccine development program.

Faced with significant product development challenges commonly associated with vaccine development programs — problems in small-scale expression of promising antigens, yield, purity, stability of proteins during process development, scale-up to cGMP manufacture, sterility after during cGMP manufacture, and stability of the recombinant proteins over time — The George Washington University researchers learned to explore alternative technologies, including bacterial, insect cell and plant-based expression systems. While these alternative systems present regulatory challenges, the team has found that it can perform detailed risk assessment analyses to minimize delays in the transition to the clinical development phases.

Major challenges during the research and development phase, including how to determine what vaccine antigen candidate is ready to transition into the product development, led to complementary scientific approaches. HHVI and The George Washington University pursued activities in addressing the expression and purification of a soluble form of one of the lead antigens in high yield, while Queensland Institute of Medical Research took a second approach, using a panel of monoclonal antibodies to target early evaluation, characterization and ranking of candidate antigens. The staff at Queensland Institute of



Hookworm research work being conducted at the Belo lab in Brazil

Medical Research also pursues and evaluates alternative methods to challenges encountered during antigen discovery and early feasibility of expression, which is generating and maintaining supporting data for the antigen candidate pipeline.

An absence of vital data required the London School of Hygiene and Tropical Medicine team to conduct a thorough quantitative assessment of the global hookworm disease burden before it could provide a cost-effectiveness analysis for the hookworm vaccine.

Approval to begin clinical testing of an investigational vaccine in the developing world is a multi-step process. For example, in Brazil the process requires regulatory approval by ANVISA, Brazil's equivalent to the U.S. Food and Drug Administration, and ethical approval by a local ethical review committee affiliated with the institution where the research is conducted, and by CONEP, Brazil's national ethical review committee.

FIOCRUZ has learned that functional working relationships with oversight agencies and continued open communication can help partners successfully achieve downstream project milestones.

As for a successful transfer of product development processes to organizations such as Instituto Butantan, the partners found that a framework for operational management and careful technical planning can overcome issues with quality control, the ability to achieve goals and objectives efficiently and economically, which can often become stalled by evolving ethical and regulatory requirements, as well as inconsistent standards, practices and criteria.

“We created this framework to enable the shift from a largely academic program focused on discovery and research to a program focused on development and rapid movement of a

promising vaccine candidate from the bench into clinical testing in humans,” Brown says. “The operational management and technical planning are tools that we have had to use to effectively manage a varied set of partners to focus on a common goal. We tend to avoid getting caught up in ethical and regulatory requirements and inconsistent standards by staying actively involved and engaged in both realms.”

Shaw and Bottazzi are kept abreast of changes through their Brazilian colleagues at FIOCRUZ and Instituto Butantan, which allows them to respond accordingly. They've found this often leads to an additional set of questions, but it keeps the important dialogue moving forward.

Open communication and realistic timelines also can overcome significant delays in timelines and milestones due to regulatory requirements, which initially hindered the prompt exchange of materials between the Institute of Parasitic Diseases and The George Washington University.

HHVI's Global Access Roadmap

The HHVI partnership has developed a strategy that is designed to permit the rapid deployment of the human hookworm vaccine to the developing world once efficacy has been shown. It emphasizes:

- A global health solution available at affordable prices to those most in need in the developing world
- Knowledge gained through discovery that is promptly available to the global scientific community

“The Human Hookworm Vaccine Initiative is the story of the struggle of developing products and technologies in the United States for the transfer to developing countries for manufacture and clinical testing in the near term and building capacity for the entire vaccine development process for the long term,” says Brown.

Adds Bottazzi, “When we first started doing our first HHVI viability assessments, we recognized that this endeavor to develop a vaccine for the developing world would always be a challenge. But we also recognized that if we engaged parties in both the developing and the developed world, we could overcome anticipated and unforeseen challenges.”

By David Perilstein



Faster, Better, Cheaper: New Vaccine Promises to Control Japanese Encephalitis



Lessons Learned:

- *Collaborative efforts can help facilitate the meeting of international development standards and World Health Organization prequalification requirements.*
- *Detailed epidemiologic and vaccine efficacy studies provide the justification for conducting public vaccination programs.*
- *Successful mass vaccination programs are greatly facilitated by a single-injection vaccine.*



The government of India initiated mass JE vaccination campaigns in 2006.

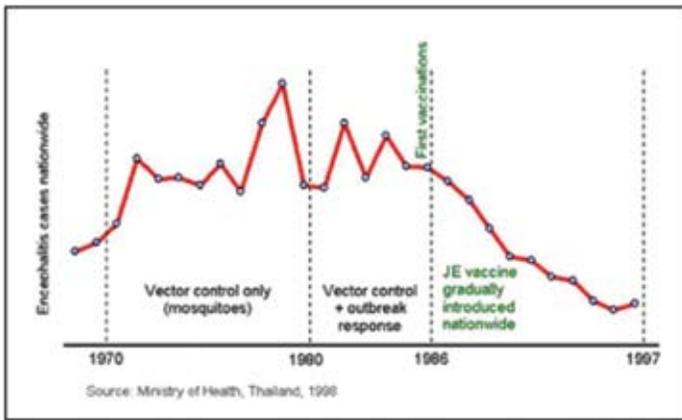
Photo provided PATH

Japanese encephalitis (JE) is caused by a mosquito-borne virus similar to West Nile fever. Epidemic to endemic in East Asia (see map), JE is the leading viral cause of neurologic disease on that continent. Some 30,000 to 50,000 symptomatic, febrile cases occur annually, mostly in children under 15 years old. There are 10,000 to 15,000 deaths among these cases. The virus is fatal 30 percent of the time when it invades the brain. At least half the survivors suffer permanent intellectual or motor impairment. There are no antiviral treatments available.

Mosquito control has not proved effective in reducing JE's disease burden, largely because the *Culex* mosquito that spreads JE is very widespread — its breeding areas include irrigated rice paddies. It also has a 10- to 12-day replication cycle; spraying would have to take place in each cycle. A vaccine for JE was invented in the 1940s, but supplies have always been limited and comparatively

expensive. (Immunization costs from \$12 to more than \$300 per dose depending on the country.) In addition, this vaccine is not very immunogenic; it requires three vaccinations for high-level protection plus boosters every year or two. The vaccine, composed of mouse brain-derived inactivated virus, carries with it the risk of serious allergic reactions as well as neurologic side effects. Still, sustained vaccine campaigns, where conducted, have been successful in controlling JE (see graph, next page).

An alternative JE vaccine appeared in 1988. It was produced by several Chinese manufacturers including the Chengdu Institute of Biological Products (CDIBP). This live, attenuated vaccine, known as SA 14-14-2, requires only one or possibly two vaccinations to provide long-lasting protection. Despite its advantages, distribution has been largely restricted to China. The Chinese pharmaceutical industry has historically concentrated on its huge domestic market, which annually consumes 50 million doses of SA 14-14-2. According to Lingjiang Yang, CDIBP's manager for international business and cooperation, "We wanted to internationalize the



vaccine from the very beginning. We went to international meetings, and we consulted with the WHO [World Health Organization]. We received licenses for South Korea and Nepal and conducted studies there.” Yet progress was slow until Chengdu entered a partnership with the Seattle-based nongovernmental organization PATH.

PATH Provides the Missing Ingredient

PATH started in 1977 with a mission to bring new contraceptive methods to women in poor countries. It has since expanded to other health issues and has a network of offices around the world. Its current budget approaches \$200 million per year.

One of PATH’s interests is in vaccine development and distribution. The organization received a 1998 grant from the Bill & Melinda Gates Foundation to support its Children’s Vaccine Program, which worked on improving childhood immunization options for a broad range of diseases. PATH’s JE project grew out of that effort. In 2003, the project received its own Gates Foundation grant. (The grant ultimately totaled \$35 million spread over six years.)

“We first targeted disease awareness because JE was seriously underdiagnosed,” recalls John Wecker, the JE project’s current director. “We did epidemiological surveillance, bringing in new diagnostic technology. Surveillance is critically important in advocacy because countries are often unaware there is a problem until faced with the data.”

Then it was a question of finding a suitable vaccine. Although there were several new JE vaccines under development, the only one ready for mass immunization campaigns was CDIBP’s SA 14-14-2. The program’s staff visited Chengdu in 2004 to discuss the vaccine’s status with CDIBP officials. China, Nepal and South Korea had approved CDIBP’s vaccine, but the question remained whether the previously collected data and the present manufacturing facility met international standards. Without national regulatory

approvals, the vaccine could not be distributed in other countries. CDIBP wanted the vaccine to receive prequalified status from the WHO. Prequalification would allow international donor agencies to purchase the vaccine for public programs in developing countries. PATH was already working closely with WHO on JE epidemiology, and this interchange expanded to include studying the CDIBP vaccine.

“PATH offered to conduct clinical trials and help build a new WHO-compliant production facility. In turn, CDIBP agreed to a very good price. It was a win-win situation,” says Mansour Yaïch, the JE project staff member responsible for the relationship with CDIBP.

The 20-year price contract that PATH negotiated with CDIBP in 2005 to 2006 covers vaccination programs in countries with a per capita gross national product of less than \$1,000 per year. There are 14 Asian countries at this low level, including India. CDIBP committed itself to providing the vaccine at a specified minimal factory-gate price for these countries’ public vaccine programs. “The price will be similar to the measles vaccine, 20 cents or 25 cents a dose,” says Yaïch. The only allowed price increases are those needed to keep up with inflation and changes in currency exchange rates. Yaïch concludes, “Our agreement will enable countries to make a long-term plan for JE vaccination.”

JE Outbreak in India

PATH and CDIBP cemented their collaboration just as India was experiencing a spike in JE cases. About 1,800 JE-related deaths resulted from the late-2005 outbreak. Most of these deaths were among children living in Northeast India along the Nepal border. The striking increase in mortality put considerable pressure on the Indian government to launch an immunization campaign before the next monsoon — and mosquito — season, which lasts from June to September.

Indian manufacturers only produced the old, inactivated vaccine, and their production capacity was low. PATH, with its large pre-existing staff in India, was able to connect the national government with CDIBP. Chengdu provided 13 million vaccine doses to launch an immunization campaign the following summer. India went on to immunize 45 million children over the next three years, with the goal of vaccinating 100 million by 2011.

“The 2005 outbreak was a special case,” says Yang. “PATH put us in contact with the Indian government and assisted in gaining acceptance of the vaccine.” PATH then helped the Indian government organize the immunization campaign, including the publication of training materials for health care personnel.

New Clinical Studies

JE Project Spokeswoman Deborah Phillips says, “Our primary goal was to empower the countries to decide whether JE vaccination programs were suitable for them.” The Indian situation helped PATH and CDIBP do just that. It provided a large store of data on the vaccine’s efficacy and safety in a non-Chinese population.

A WHO vaccine safety committee in late 2006 reviewed safety data from the 9.3 million children vaccinated in the summer of that year and advised that the vaccine had an acceptable safety profile. Sixty-five serious adverse events were reported, including two clusters of encephalitis-like syndromes, but the committee judged that these were unrelated to the vaccine. The committee concluded by calling for further, more rigorous safety monitoring.

The Indian government set up a postmarketing study that has followed 1,400 vaccinated children. This ongoing study is monitoring the level of immunity as well as safety over the course of one year postvaccination. Another Indian study is checking whether there is any possibility that the weakened JE vaccine strain will revert to wild type and cause disease. This is a concern raised by clusters of encephalitis like the ones noted in 2006, although the WHO Safety Committee found that any link to the vaccine was unlikely. In 2005, the same committee noted that the genetic differences between the live and attenuated strain seem too great for reversion to occur.

A third study, conducted with PATH cosponsorship, is comparing the incidence of JE in a vaccinated juvenile population and a matched unvaccinated group. “We need to show the Indian government that it is getting its money’s worth. That will convince it to maintain the JE vaccination program over the long term,” observes Wecker.

PATH has carried out two clinical trials of the vaccine along with local investigators. One in the Philippines studied the ability to coadminister JE and measles vaccines (ideally at age nine months). Coadministration would be a great convenience for vaccination programs and parents alike. There is, however, a concern that concurrent vaccination will interfere with the immune responses to each vaccine. The WHO committee in 2005 asked for more information on this question. The Philippines trial enrolled 600 children and randomized them to receive both vaccines either separated by a month or together. The results indicated some interference with the measles vaccine response at one month postvaccination. There were no differences between trial arms after one year. PATH continues to follow participants and measure long-term protection.

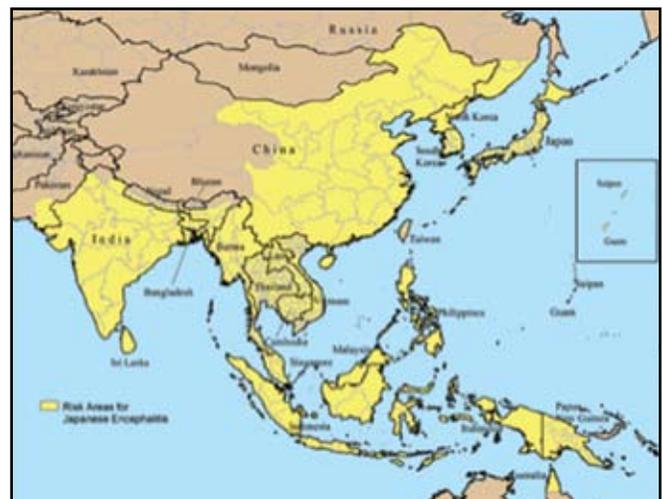
Another issue raised by WHO involves the interchangeability of the live and inactivated vaccines. Many children have received the inactivated vaccine, which requires frequent boosters. What happens if the live vaccine is given instead of the booster? Using the live vaccine might prove better or worse as a booster. A PATH trial in Sri Lanka is studying this question in 570 Sri Lanka children previously vaccinated with the inactivated JE vaccine through that country’s extensive JE immunization program.

Boosting Production Capacity

CDIBP’s original manufacturing plant for the SA 14-14-2 vaccine left several things to be desired. One, it did not have the extra capacity to satisfy international demand. Two, it did not meet the WHO’s stringent standards for good manufacturing practices (GMP). The vaccine could not receive WHO prequalification until those standards are met.

The WHO GMP manual is 400 pages long. It covers the range of pharmaceutical products, giving detailed descriptions of manufacturing practices that best ensure high-quality products that are free of contamination. Plant design — including cleanliness and hygiene, inspection and testing, packaging and labeling, and storage — has to take GMP goals into account. Job descriptions and production procedures have to be documented in detail, with personnel carefully trained to fulfill their assigned tasks. Lastly, there has to be meticulous documentation at every step that the proper practices were followed.

With technical support from PATH, CDIBP undertook the construction of a completely new plant for the expanded production. CDIBP financed the construction, and PATH in 2007 contracted with a French engineering company, Technip, to



Geographic distribution of Japanese encephalitis

Source: U.S. Centers for Disease Control and Prevention

manage design, construction and equipment acquisition to meet GMP standards. PATH also hired a number of consultants to advise on vaccine manufacturing.

Yang says, “In China nobody has achieved GMP standards. We will be first. This accomplishment is very important for the Chinese vaccine industry. It will be a model for other companies.”

The facility was supposed to open in 2008 but was delayed by the earthquake that year in Sichuan. As of the summer of 2009, the completed plant was undergoing validation testing and refining its manufacturing practices. The WHO-required GMP documentation was in process, too. CDIBP’s engineers meanwhile were planning the shift of production from the old to the new facility. When online, the unit will be able to produce 50 million vials a year, with each vial containing one or five freeze-dried vaccine doses.

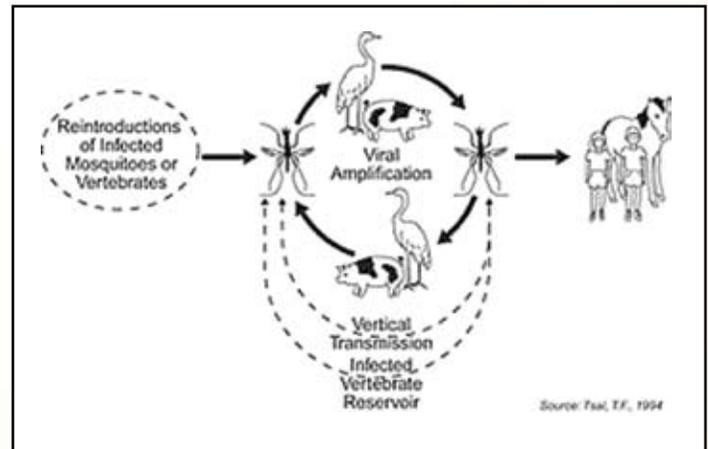
Toward Control of Japanese Encephalitis

This partnership has run smoothly so far, not counting the earthquake. The main issues were that the CDIBP was not capable of collecting the data needed for WHO prequalification, nor could it build a high-capacity plant on its own that would meet WHO’s GMP standards. PATH provided funding and expertise to achieve these two ends. The main hurdle was negotiating the details, including the guaranteed price. But the goal of expanding distribution of the Chinese JE vaccine suited CDIBP as much as PATH, so there were no real disputes. The test of the agreement’s durability will come in the course of meeting high demand for the vaccine over the years

PATH’s JE grant from the Gates Foundation ends in 2009. The organization’s role will be diminished after that, but it will still contribute to advancing the vaccine. “Next year will be very critical,” says Yang. With PATH’s assistance, CDIBP plans to apply for WHO prequalification in 2010. By the end of 2009, it will meet with WHO officials in Geneva to go over its plans. The pricing agreement with PATH will remain in force until 2026. A joint PATH-CDIBP steering committee that meets annually will review vaccine issues.

PATH’s Yaïch concludes, “For me this is really a South-South partnership involving China, India and other Asian countries. It will be self-sustaining. The PATH project is ending except for some residual regulatory activity. Then the company and the countries will be on their own.”

Countries that need assistance in funding and launching immunization programs can obtain it from a number of international and national aid programs, including USAID, UNICEF and the Global Alliance for Vaccines and Immunization (GAVI). Unlike polio or small pox, JE will persist even if there is universal vaccine coverage. The virus establishes “amplifying” populations in animal hosts, notably pigs and wading birds, which support the disease’s spread (see figure below). Human vaccination will be necessary in high-risk areas for the foreseeable future.



Japanese encephalitis transmission cycle

Source: TF Tsai 1994, via PATH

Three other JE vaccines — sponsored by large European and Japanese pharmaceutical companies — are in advanced development. In 2009, one of these, an inactivated version of the SA 14-14-2 strain, received regulatory approval in the United States, Europe and Australia. The new vaccines are expected to initially fill a different marketing niche than CDIBP’s product. Yaïch says, “CDIBP has a very affordable price. The other vaccines will come to market at \$10 or \$20 per dose in developing countries. Their producers are targeting middle-class populations that receive their vaccines in the private sector. These companies will not start with the production capacity that CDIBP has.” If their prices eventually become competitive, the new vaccines will add to the tools available for public JE control programs.

PATH is establishing an international JE working group with WHO and other organizations associated with the JE project. The working group will provide a permanent platform for promoting JE vaccination. Japanese encephalitis vaccines have come a long way since the 1940s. Keeping the disease under control will nevertheless require a sustained effort. With the technical and economic issues resolved, the sustainability of political will is now the prime question.

By David Gilden

Multi-Pronged Attack on Cervical Cancer Detection Seeks to Speed Detection and Treatment in Resource-Constrained Countries



Lessons Learned:

- *Because of differences in stakeholders' organizational styles and cultures, agreement on a clear, common purpose is critical to a successful collaboration and ongoing knowledge sharing may require continuous effort.*
- *Inadequate funding can leave individual partners stretched too thin and thus slow results.*
- *Helping local medical communities recognize the advantages of new health care technologies will enable effective rollout.*



ACCP, CCA, PATH and others agree that the best strategy for rapidly reducing deaths due to cervical cancer is a comprehensive prevention approach, focusing both on screening of adult women and vaccination of adolescent girls.

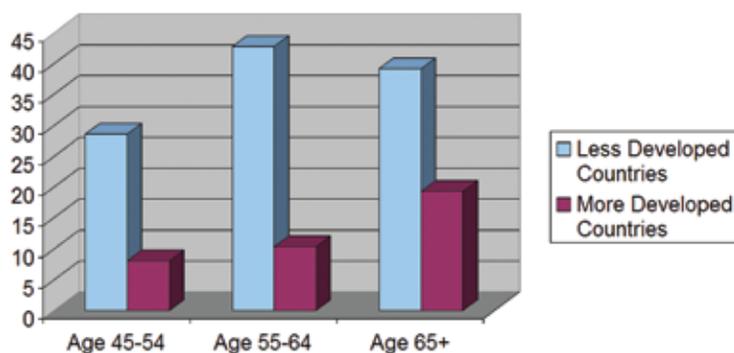
Cervical cancer kills approximately 270,000 women each year with nearly 85 percent of those deaths in resource-poor settings. Routine cytological screening of women, commonly known as the Pap smear, has resulted in a dramatic decline in cervical cancer deaths over the past four decades in wealthier regions. However, screening has been much less successful in developing regions. A key reason for continuing high mortality in the developing world is the shortage of practical and cost-effective, yet still high-quality, precancer screening programs. Existing tests are prohibitively expensive and too technical for low-resource settings.

New technologies that allow alternative screening methods could help overcome this obstacle. To this end, PATH developed close partnerships with several, very different organizations to launch a multi-pronged approach to solving the problem.

In 2000, an effort to investigate sustainable alternatives to Pap became the Alliance for Cervical Cancer Prevention (ACCP); member organizations included EngenderHealth, the International Agency for Research on Cancer (IARC), Jhpiego, the Pan American Health Organization (PAHO) and PATH, which acts as the coordinator. Recently the alliance expanded to include three additional members. The ACCP, with support from the Bill & Melinda Gates Foundation, worked closely with the World Health Organization, Harvard University, and governmental and nongovernmental partners in Africa, Asia and Latin America on a coordinated research agenda aimed at assessing a variety of approaches to cervical cancer screening for low-resource settings. The goals were to improve service delivery systems, ensure that community perspectives and needs were incorporated into program design, and heighten awareness of cervical cancer and effective prevention strategies.

After initial friction generated by competitive natures and role misunderstandings, the details of a clear, common purpose and

Age-Specific Cervical Cancer Mortality Rates per 100,000 Women



Source: Globocan 2002

Many more women die of cervical cancer in the developing world than in wealthier countries. In the industrialized world, effective screening programs help to identify precancerous lesions at a stage when they can easily be treated. But lack of screening programs in poorer countries means that the disease is not identified until it is too late, resulting in higher mortality.

roles for each partner were negotiated and carefully articulated over the first couple of years to help coalesce the ACCP. Trust between the partners built over time, making it easier to resolve issues as they arose. The group also agreed early on to operate under the single Alliance logo, rather than vie for positioning of their separate logos, which has helped build cohesiveness. Even so, partners are listed individually in the body of documents and printed materials so that some individual recognition is retained.

In the nine years since inauguration of the project, the ACCP partners conducted studies comparing a number of screening techniques including cytology (Pap), visual inspection methods with acetic acid (VIA) or Lugol's iodine, and a HPV DNA test. The tests were evaluated in more than 20 low-resource settings around the world.

VIA and HPV DNA testing have proven to be of special interest. The ACCP found that VIA compares well to cytology in terms of sensitivity for disease detection, yet presents clear advantages because it requires fewer specialized personnel and less infrastructure, training and equipment. Cervical cancer screening using VIA can be offered in remote, less-equipped clinics, thereby reaching more women. Another important advantage is that VIA provides immediate results, making it possible to screen and treat women during the same visit. Immediate treatment means that women do not have to make an extra visit to the health center — this reduces the number of women who are lost to treatment

because they cannot return for one reason or another. Even so, recent data suggest that a new, low-cost HPV test specifically designed for low-resource settings has much better performance than either cytology or VIA (see below).

In 2003, PATH launched a second related initiative: the Screening Technologies to Advance Rapid Testing (START) project designed to develop two different biochemical HPV screening methods appropriate for use in the developing world, including the low-cost HPV DNA test previously mentioned. It was important that the tests be acceptable to women and their providers, relatively simple to use, accurate, and affordable; cultural sensitivities to medical tests being performed on the genitals or by male doctors on female patients were of concern, therefore the testing method had to be made acceptable to the population. In addition, diagnosis and treatment, if indicated, should be possible during the same screening visit.

In this effort, PATH developed close partnerships with the commercial medical diagnostics company Digene, since purchased by QIAGEN, and the World Health Organization (WHO). Digene/QIAGEN needed access to cervical smear samples from countries of interest, and needed PATH to manage field research with local institutions.

PATH needed an industry partner to develop the technology and for future manufacturing and distribution of the test. WHO, a research and advocacy partner, was keenly interested in technologies that could bring precancer screening to poor women. Further, WHO plays a regulatory role, and will assess the new test

ACCP project areas



for international procurement by United Nations (UN) agencies, such as the United Nations Population Fund, and will prequalify the manufacturer of the product — thus significantly increasing access to the test worldwide.

PATH is also partnering with Jhpiego, a not-for-profit agency affiliated with The Johns Hopkins University, to lay the foundation for future introduction of the new test through creation of a network of in-country training excellence centers focused on VIA and cryotherapy.

By early 2007, PATH and QIAGEN had developed and field-evaluated a new, highly sensitive HPV DNA test that is portable, could be powered with rechargeable batteries and uses reagents that do not require refrigeration. Test results are available in less than two-and-a-half hours, facilitating immediate treatment or referral in the same visit.

In developing countries, however, several challenges impede widespread adoption of new technologies. Before incorporating the HPV DNA test into national cervical cancer prevention strategies and plans, ministries of health need evidence that the new test is feasible and appropriate for their health system infrastructure and their geographic, cultural and economic circumstances. In addition, private industry needs guidance in navigating the complexities of product introduction in the public sector of developing countries, which are generally perceived as high-risk, low-return markets. To address these issues, in November 2007, PATH inaugurated a follow-up project to START, called START-UP.

And Then There Were Three

Cervical Cancer Action (CCA) is yet a third coalition of organizations with diverse connections to the prevention of cervical cancer in the developing world, specifically to immunization, cancer, sexually transmitted diseases and reproductive health, women's health, and HIV/AIDS. This group coalesced to advocate for equitable and rapid access to new lifesaving technologies to prevent cervical cancer in these countries, specifically better and less expensive methods of screening adult women for signs of pre-cancer and provision of HPV vaccines to protect girls.

CCA was created in 2006; founding members include PATH, PAHO, the American Cancer Society, the International Planned Parenthood Federation, Cancer Research UK, the International Union Against Cancer, the AIDS Vaccine Advocacy Coalition, the International AIDS Vaccine Initiative, and the International Federation of Gynecology and Obstetrics. CCA has been designed to avoid duplicating the activities of any member organization or taking

on activities that member organizations, or other groups, are better able to fulfill. The work of CCA is grounded in public health science, but also evokes arguments related to economics and global equality of access.

The CCA partners recognized that, unless there is coordination and cooperation on a common, forward-looking mission to ensure access to the new tools, the potential for real progress in reducing the global burden of disease will be unfulfilled.

Certain conditions must be in place for these new prevention technologies to become available and be effectively used in developing countries:

- Strong scientific and public health leadership by leading international health agencies and organizations
- Sustained political leadership and financial commitment for a comprehensive approach to appropriately and effectively vaccinate girls and screen and treat women
- Partnership among diverse constituents of civil society, health professionals, medical associations, researchers, donors and governments to support widespread access to these new tools
- Adequate supplies of the full range of HPV and cervical cancer prevention tools from the manufacturers at affordable prices
- Leadership and action by multi-lateral agencies, including rapid prequalification, issuance of international guidelines and large-scale procurement for developing countries.

CCA activities have been limited by its funding model. It has not been able to raise external funding but instead functions on cash and in-kind contributions from CCA Governing Council members. Lack of external funds may be, in part, a result of the decision early on not to solicit or accept funding from the pharmaceutical industry, even though CCA members felt that such funding may have been relatively easy to access. The Governing Council adopted this position to avoid any perception of conflict of interest in its mission.

The funding CCA has obtained from some of the nine Governing Council members over the past two years has been used to support a small but very active secretariat. CCA members recognize the utility of maintaining a dedicated secretariat, but it is unclear how sustainable this shoestring budget system will be in the future.

Aside from the efforts of the secretariat, all CCA work is carried out by members of the CCA Governing Council. These volunteers have primary duties that sometimes force them to put CCA tasks at lower priority. It is more difficult for some members to allocate time to CCA than for others.

Challenges of the Three Efforts

The three initiatives share goals but incurred separate challenges; some obstacles were due to the nature of the partnership, others were due to the nature of the work.

In the case of the Alliance for Cervical Cancer Protection, the groups were brought together because of their interest in cervical cancer prevention in the developing world, but not necessarily because they were driven to work as part of a strong alliance. A lack of attention to the collaborative/coordinated work of the alliance in the early days led to friction — ACCP scientific and programmatic discussions often were contentious and maintaining the partnership seemed in doubt on several occasions.

For example, while some of the partners had more of a research perspective, others were more focused on practical programmatic approaches. This led to different tolerances for uncertainty in the data related to use of visual inspection as a primary screening method and use of a single-visit approach to screening and treatment. Partners were also influenced in part by the prevailing opinions and political climate of the regions where they worked. It is possible that ACCP achievements could have been more extensive had the partners agreed at the start to a coordinated research agenda. However, given early differences in organizational visions, the ways that the funding was dispersed and individual personalities, agreement on an overall agenda did not seem likely.

Over time collaboration became easier. As the evidence base grew during the following years, the partners defined their respective roles and became accustomed to working together. In short, trust levels increased, and the ACCP's collective vision became more aligned. By 2007, ACCP partners were able to articulate and broadcast a clear set of 10 recommendations endorsed by all.

The ACCP is now exploring how a cervical cancer screening visit can serve as a core building block for a broader menu of health services needed by women in their 30s and 40s, such as screening for cardiovascular disease, breast cancer, and diabetes; management of symptoms of menopause; and other services largely unavailable in developing countries, but which address increasingly important public health problems.

The START program initiative and its sequel, START-UP, faced a number of obstacles. A key challenge for QIAGEN, the industry partner, is to develop a business model that allows the marketing of two types of HPV DNA tests — one more technologically complex than the other and, thus, with different pricing tiers — in different parts of the world.

Another key challenge came from medical communities. One aspect of country mobilization is engagement of the community of reproductive health care providers in the country, including the obstetrics-gynecological community. These clinicians and researchers, many of whom are very comfortable with Pap smear testing in urban settings, may see Pap and subsequent diagnosis as gold standard medicine and may, in fact, make a living from cytology. Many have not seen the results of alternative strategies with their own eyes and remain skeptical about those alternatives.

To address these needs, PATH, Jhpiego and WHO are continuing to promote their findings in professional journals, at international meetings and through personal contacts in the hopes of moving influential professionals towards a new paradigm of cervical cancer screening in low-resource settings.

For Cervical Cancer Action, progress toward comprehensive prevention and control has been substantial, despite key challenges including the high current price of HPV vaccine in the private sector and lack of global success implementing large-scale cervical cancer screening in low-resource settings. However, the GAVI's recent interest in subsidizing HPV vaccine and encouraging results using less-expensive and more rapid screening tests is galvanizing the effort. The global conversation has evolved to the point that country-focused discussions can become a major theme over the next few years.

Coming to Agreement

Some member organizations are constrained in the kinds of agreements they can sign with others. This is especially true of UN agencies. It is for this reason that neither WHO nor IARC felt they were able to join the coalition. UN member PAHO was able to join, but cannot enter into some of the agreements shared by all other groups. The coalition has had to craft agreements to accommodate these circumstances accordingly.

By Pam Baker

Links for Life Integrates Programming for Food Security, Nutrition and HIV/AIDS



Lessons Learned:

- *Knowledge sharing through “learning communities” is the key component to integrating programs that can affect change.*
- *Success depends on participants having the mechanisms to regularly explore ideas, think together and share relevant knowledge across local, regional and national boundaries.*
- *A program dependent on volunteers is challenged by inconsistent levels of participation.*



Photo by Shutterstock® Images

The epidemics of HIV, hunger and poverty are inextricably linked. Throughout Africa, these singularly threatening assaults have converged to form a perfect storm that affects the lives and livelihoods of individuals and inhibits families and communities from taking care of their most vulnerable members.

Good nutrition has been called the key to positively living with the HIV virus. When malnutrition prevails, the immune system is weakened and susceptibility to infections increases.

“Although antiretroviral therapy (ART) is becoming increasingly available, treatment can fail when patients are nutritionally compromised,” say Gwenelyn O’Donnell-Blake, food security technical officer at Project Concern International (PCI). “Without nutritious food to complete treatment, patients are often too ill to successfully start ART. And, once on treatment, interruptions due to hunger contribute to treatment failure and drug resistance.”

To promote learning and advocacy around integrated HIV and food/nutrition security (FNS) programming, PCI and its many nongovernmental organization (NGO) partners initiated Links for Life, a multi-faceted development program.

Communities of Practice

Links for Life was conceived at the Africa Forum 2006, a gathering of NGOs and international health and development organizations from across the continent. A total of 220 practitioners from 16 countries attended this hands-on, skills-building conference that focused on sharing up-to-date knowledge in integrated HIV and FNS programming.

In June 2006, groups of practitioners that attended the Africa Forum started meeting to continue sharing their experiences with integrated programming in their own countries. Without formal support and funding for these meetings, efforts toward continuous sharing were short-lived. These efforts, however, led to the Links for Life Communities of Practice (CoPs), which is currently being piloted in Ethiopia and Malawi.

What Is a Community of Practice (CoP)?

A community of practice (CoP) is a group of people who share a concern, set of problems or passion for a topic, and deepen their knowledge and expertise by interacting and learning from one another on an ongoing basis. CoPs can be formal or informal, related to a career or a personal interest or hobby.

Natalie Campbell, (former) technical advisor at CARE USA, uses a group of pregnant women as an example of a CoP. These women get together on a regular basis; they share their thoughts, ideas, complaints, joys and, just as importantly, the lessons they have learned to help them cope with this nine-month period of their lives. These women are unknowingly engaging in an informal CoP.

More formal versions of CoPs are used by major international organizations to propagate learning. For example, over the past decade, industry leaders such as Chrysler, McKinsey & Co., the World Bank and others have relied on CoPs to stimulate innovation, develop social capital and nurture emerging knowledge.

An important distinction must be made between CoPs and working groups or task forces. The latter two are brought together by obligation to an employer to create a product or meet a goal. CoP participants, on the other hand, take part voluntarily. They share and learn because they are passionate about the topic at hand, and it helps them to improve their abilities around their practice or discipline, whether it be career-oriented or simply a personal interest. They are self-motivated to attend meetings, take part in discussions and share their own knowledge and skills.

Since participation is voluntary, it is crucial that CoP meetings be engaging and fun for participants. CoP members must see value in being part of the group and understand the relevance of their participation and that of their peers. Only with dedicated members, strong internal leadership and a spirit of sharing knowledge, will a CoP be successful and sustainable.

These two CoPs, also known as “learning communities,” promote organizational learning and help identify emerging practices in HIV and FNS programming in Ethiopia and Malawi. Led by experienced facilitators hired by Links for Life, CoP members from NGOs, government and academic institutions working in HIV and FNS programming meet to share their programmatic experiences and to document what they are learning from being part of the CoP.

One of the first steps toward establishing the Ethiopia and Malawi CoPs was to set up the Steering Committee to oversee the communities’ inception and nurture their development. The committee first convened for a strategic planning session in September 2007 via a teleconference led by O’Donnell-Blake. The committee developed the concept, put together a fundraising plan and formulated a timeline for the initiative. Steering Committee members include international NGOs and academic and research institutions that work in HIV, food and nutrition security and are also committed to promoting “integrated” HIV and FNS programming. (A full list of Steering Committee members appears near the end of this article.) Partners spent the next few months securing funds to support the CoPs.

By April 2008, the Links for Life CoPs were up and running. Practitioners attended regular meetings and learning events where they decided on criteria for identifying promising practices in integrated programming and set out to review some of their own projects, as well as projects implemented by nonmembers. They interviewed project staff and beneficiaries and reviewed monitoring data to assess whether projects were sustainable, exhibited social acceptance by their community, were cost effective, empowered beneficiaries, addressed the underlying causes of poverty and met other specific criteria set by CoP members.

“The most beneficial aspect of the CoPs is being able to gather technical implementers from the same country to look at what is working well,” says Tina Lloren of Save the Children Federation. “[The CoPs have] strengthened the collaboration among in-country networks. Equally important, the lessons learned will be shared at the Africa Forum 2009, thus spreading the wealth of knowledge beyond the countries’ borders.”

Bringing It All Together

For these CoPs to be successful, participants need mechanisms to explore ideas, think together and share relevant knowledge. This took collaboration at global, regional and country levels.

About 45 organizations are involved with Links for Life, globally as Steering Committee members and locally as CoP participants. Organizations not only provide financial support, but also facilitate their CoP member participation by allowing their staff to attend meetings, engage in CoP-related activities and host CoP meetings on a rotating basis.

To ensure CoP member participation and to guide the formation of the groups, PCI and the Steering Committee hired a country coordinator for each of the two countries. These individuals are skilled facilitators and are dedicated to sharing and documenting knowledge in integrated HIV and FNS programming.

During the early stage of developing the CoPs in Malawi and Ethiopia, the CoP coordinators devoted significant energy to securing commitments from CoP participants in each country. Since participation is voluntary, the program relies on its perceived value to each and every member and his or her organization. Initially, country coordinators had a hard time getting participants on board.

“The biggest challenge for Save the Children has been finding consistent and dedicated staff to give the CoP the time it needs and deserves,” said Lloren.

Success Follows Reconciling Challenges

Natalie Campbell, then technical advisor at CARE USA, traveled to Ethiopia and met with both country coordinators in July 2008. She cofacilitated a learning event for members where, as part of an exercise, participants asked themselves why they attended CoP meetings. Without an obvious product to produce, as they were accustomed to, participants did not immediately see the value of CoP membership. For many, the answer to this question has evolved over time.



Ethiopia CoP's monthly meeting

“It’s important that the country coordinators are passionate and people-oriented,” says Campbell. “And, they need to be dedicated to their “domain” — the CoP term for the topic or theme that brings members together.”

Because a tradition or culture of sharing knowledge across agencies, especially between those who compete for similar funding and prestige does not automatically exist, trust between CoP members initially posed a challenge. Over time, however, meetings and learning events used participatory learning tools and methods to create an environment that built trust and facilitated sharing and collaborative learning. This has gone a long way toward encouraging members to engage and invest in the CoP. Participants have articulated tangible and intangible benefits to belonging to their CoP.

To bolster trust, each meeting begins with one organization sharing its recent programming successes, as well as challenges. Participants are encouraged to bring specific issues to the group for peer-assist exercises in which members brainstorm ideas to help others with specific problems. When members see that their peers have valuable solutions, they are more inclined to continue participating.

Links for Life CoP Steering Committee

Current Steering Committee members include Academy for Educational Development, ACDI/VOCA, Action Against Hunger, Africare, Association of Nutrition Service Agencies, CARE USA, Catholic Relief Services, Christian Relief and Development Association, Concern Worldwide, Consultative Group on International Agricultural Research, Family AIDS Care Trust, Friends of WFP, The George Washington University, Global Alliance for Improved Nutrition, Global Food and Nutrition, GTZ, Helen Keller International, Kalusha Foundation, Land O’Lakes, Mercy Corps, Nzinga International, Oxfam, PATH, Project Concern International, Save the Children, UNDP, USAID, U.S. Department of State, World Vision, and the World Food Program.



Ethiopia CoP members engage in small-group work.

Another challenge to establishing and sustaining CoPs involved relying exclusively on electronic communication. Since broadband Internet access is inconsistent at best, coordinators have learned to rely on handwritten communication and text messaging via cell phones to remind participants of meetings and convey other urgent messages. Additionally, Yahoo!® Groups were established as an online discussion forum and repository for meeting minutes, photos, CoP reports, calendar of events and other documents of interest to members.

Process not Product

Early successes are evident, but a healthy CoP is a process, not a product. Before success can be claimed, members will have to continue to nurture and cultivate their learning communities. A future challenge will be how to sustain and grow CoPs long-term. Convincing organizations that learning requires resources and does not happen spontaneously will be tough. Money is also needed to support logistics of meetings, learning events and field-site visits, as well as salaries for coordinators and other support staff. Partnership and teamwork across and between all members is required for sustained success.

When it comes to coordination of the many partners brought together for this project, Campbell gives credit where it's due, "I have to give PCI, including O'Donnell-Blake, credit for being persistent and keeping everyone organized."

Campbell notes that a project leader cannot be a passive person. He or she must be able to motivate people and convince donors that this multi-organizational learning initiative is worth funding. "Without salaried coordinators in Malawi and Ethiopia, we could not have achieved what we have," Campbell says. "Internal leadership is crucial for any collaborative programmatic effort, especially for CoPs that bring individuals and organizations from diverse backgrounds together."

The promising practices identified by the Malawi and Ethiopia CoPs were showcased at Africa Forum 2009: Sharing Integrated Solutions to HIV and Food/Nutrition Insecurity in June 2009. CoP members will also facilitate sessions, for other practitioners, on lessons learned from starting their own CoP. It is hoped that their achievements will encourage other practitioners to use this unique platform — the community of practice — to promote learning in more aspects of HIV and FNS programming across Africa.

By Ashley Mastandrea

Kara Greenblott of Nzinga International and Gwenelyn O'Donnell-Blake of Project Concern International contributed to this article.

The Malawi Project: Global Assistance Initiative to Combat HIV/AIDS



Lessons Learned:

- *Hands-on experience and resources enable partners to provide technical assistance for the quick implementation of vital activities.*
- *Sustainability should be a key aspect of program design.*
- *Partner organizations can help each other and motivate existing staff by filling human resource gaps.*
- *Ministries of health should spearhead and be the public face for major global health initiatives.*



The refurbished training lab in the Malawi College of Health Sciences in Lilongwe.

Combating global HIV/AIDS received priority status in 2003 with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), which set out to build sustainable local capacity by supporting the training of new health care workers in HIV/AIDS prevention, treatment and care. Nowhere is there more need for improved HIV/AIDS diagnosis and treatment than in the eight African countries of Botswana, Lesotho, Namibia, South Africa, Tanzania, Uganda, Zimbabwe and Malawi, a fact underscored by Bingu Wa Mutharika, Ph.D., president of the Republic of Malawi, who has made management and prevention of the HIV/AIDS pandemic a top priority.

Under the aegis of PEPFAR, several governmental and non-governmental organizations (NGOs) have been developing and implementing training programs for this growing demand in prevention, treatment and care programs for HIV/AIDS. One such program is the Howard University Technical Assistance Project (HUTAP), the second five-year cooperative agreement that the Washington, D.C., university has signed with the Centers

for Disease Control and Prevention Global AIDS Program since 2002. Howard University is one of the leading partners involved in building the overall laboratory capacity in Malawi.

Into its second year of the agreement, the Howard University College of Pharmacy, Nursing and Allied Health Sciences, working in conjunction with several other NGOs, has enhanced the infrastructure that will provide a critical foundation on which to build high-performing laboratory services essential to the scale-up and success of Malawi's newly adopted five-year AIDS treatment plan, Prevention of Mother-To-Child Transmission (PMTCT) and Early Infant Diagnosis programs. To date, HUTAP has:

- Trained more than 160 laboratory technicians, tutors and managers in HIV diagnosis and disease monitoring
- Developed an HIV testing preservice curriculum
- Refurbished three training laboratories and a computer laboratory to enhance teaching and learning of the new curriculum content at two laboratory training schools
- Formed partnerships with other organizations in Malawi, including the U.S. Centers for Disease Control and Prevention's Global AIDS Program (CDC-GAP), Ministry of Health, William J. Clinton Foundation, the United Nations

Children's Fund (UNICEF), World Health Organization (WHO) and Baylor College of Medicine to rapidly expand access to HIV testing and treatment for pregnant mothers and HIV-exposed infants

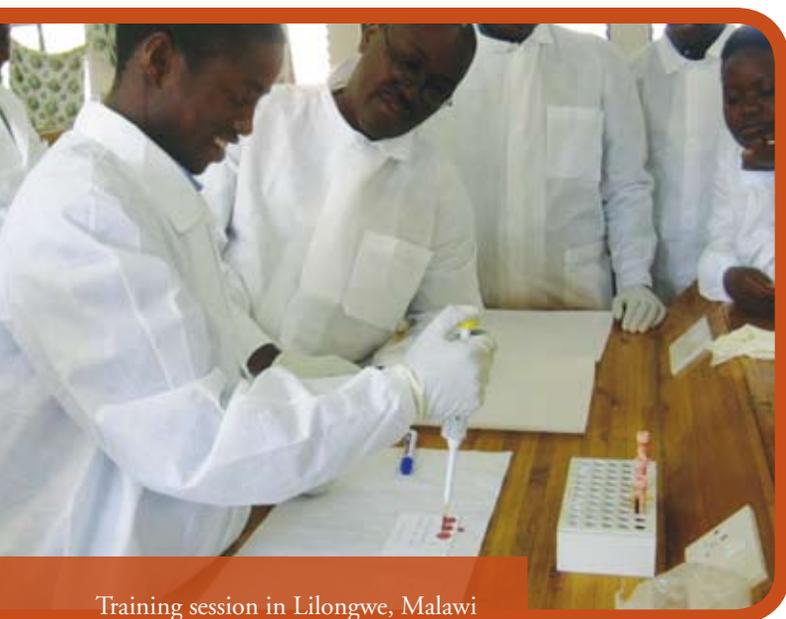
- Strengthened three referral hospital laboratories to provide early infant diagnosis for HIV using DNA PCR (polymerase chain reaction), which previously had limited use in Malawi
- Provided technical staff to address human resource gaps and provide technical assistance to assure quality lab services or strengthen management capacity

A Future Is at Stake

By the end of 2002, sub-Saharan Africa represented 29.4 million of the estimated 42 million HIV/AIDS cases globally. The enormity of this devastation caused by HIV/AIDS is best measured in the most dire of human terms — a drastically reduced life expectancy, a steadily decreasing workforce and the virtually unchecked proliferation of poverty.

The HIV/AIDS epidemic in Malawi is one of the most severe in sub-Saharan Africa, with almost one million of the nation's population living with HIV/AIDS, according to a 2008 update by the Joint United Nations Programme on HIV and AIDS (UNAIDS). The HIV/AIDS estimates for Malawi in the 2008 UNAIDS update include:

- 930,000 people living with HIV
- 11.9 percent prevalence rate in people 15 to 49 years of age
- 840,000 people age 15 and up living with HIV
- 490,000 women age 15 and up living with HIV
- 91,000 children up to 14 years old living with HIV
- 68,000 deaths due to AIDS
- 560,000 children up to age 17 orphaned due to AIDS



Training session in Lilongwe, Malawi

Organizations and Their Contributions in Malawi

Laboratory capacity and infrastructure are important in providing HIV/AIDS care and support. As more HIV/AIDS treatments become available, training institutions in sub-Saharan Africa are challenged to produce more technicians to fill job vacancies, as well as quality educational programs that address HIV testing and monitoring needs.

To strengthen the laboratory capacity for providing quality HIV testing services in Malawi, the CDC funds HUTAP as part of its activities for PEPFAR. Its primary target is to improve the infrastructure and quality of laboratory testing at central and district-level hospitals, including refurbishment, purchasing laboratory equipment, consumables and reagents in support of HIV testing and training; updating skills of laboratory technicians; and increasing human resource capacity of laboratory personnel.

Howard University has a long history of working with the Ministry of Health in Malawi and the CDC-GAP to build the country's capacity in laboratory services and infrastructure. A preservice assessment documented the need for tutors at training institutions and hospital personnel who prepared laboratory technicians for HIV work. Data were collected through surveys and focus groups on available resources, curricula content, tutor training and expertise, and skills of laboratory technicians. Site visits were made to observe laboratory operations.

The results supported the need to upgrade the laboratory curriculum; provide the laboratory training institutions and hospital laboratories with equipment, reagents and supplies; and upgrade the knowledge and skills of tutors, lab supervisors and technicians.

HUTAP is managed in Malawi by Carol Porter, Ph.D., assistant professor, Department of Clinical Laboratory Sciences in the Division of Allied Health Sciences at Howard University. She is assisted by several local Malawians involved in day-to-day activities to address identified needs, and several members of the Howard University faculty in the College of Pharmacy, Nursing and Allied Health Sciences provide assistance to the project. The team is responsible for:

- Strengthening in-service training, supervision, management and quality-assurance programs
- Updating preservice training curricula to link it to target testing for HIV diagnosis, disease monitoring and opportunistic infections
- Bringing trainers and clinical instructors up-to-date on new HIV curriculum content, educational methodology and curricula implementation

- Creating laboratory centers of excellence at service-delivery sites for HIV testing
- Recruiting and retaining senior-level staff to fill the lab positions being created to implement national quality-assurance programs for HIV, CD4 (cluster of differentiation 4) and PCR.

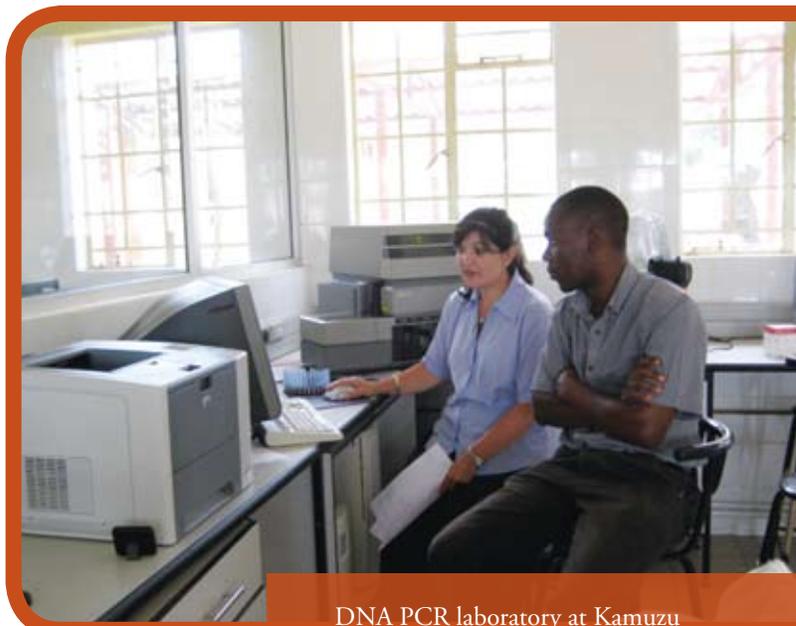
“Howard University is working to build the critical laboratory infrastructure in Malawi; educating trainers, clinical instructors and lab technicians; hiring staff; implementing quality-assurance programs; and helping with supplies,” says Porter. “But one partner can’t provide everything to make a program of this magnitude successful.”

Also joining Howard University in the CDC-funded University Technical Assistance project are the William J. Clinton Foundation, which provides the DNA PCR and CD4 test kits and supplies and started a lab assistants training program in 2007 to address the shortage of lab personnel (the first class of 80 students will graduate in 2009); Abbott Funds; and Baylor International Pediatric AIDS (BIPAI) at Baylor College of Medicine in Houston, which provides clinical services, recruits pediatricians, treats infants and mentors Malawian health staff.

The Baylor College of Medicine-Abbott Fund Children’s Clinical Centre of Excellence (COE) was officially opened in 2006 within the grounds of Kamuzu Central Hospital in Lilongwe, Malawi. It serves as the outpatient pediatric HIV clinic for the hospital and a pediatric referral center for the nation.

“Baylor’s mandate in Malawi is to assist the Ministry of Health in the national effort to improve pediatric HIV care, which we do through this collaboration [and] that uses each partners comparative advantage,” says Peter N. Kazembe, M.D., chief of pediatrics at Kamuzu Central Hospital and director of Malawi’s first center for the care and treatment for children with HIV/AIDS. “Baylor brought its expertise in clinical training to the initiative, while Howard brought to the table its expertise in lab training, management and monitoring, which were critical to developing new skills that government hospital lab technicians needed to diagnose the DNA PCR tests for babies under 18 months old.”

In just over two years of operation, Kazembe says clinical services staff have registered more than 3,400 patients at the COE. This figure does not include the children who doctors are managing in the outreach sites (district hospital and health centers), where they are operating nationally. From its inception, the number of children accessing care at the COE has progressively increased to where it is now enrolling about 100 new patients per month; the daily patient attendance ranges from 50 to 100. The COE has an active caseload



DNA PCR laboratory at Kamuzu Central Hospital lab in Lilongwe

of 2,100 patients, with 1,039 of them on anti-retroviral drugs. In line with the family-model of approach to HIV care and treatment that is being pioneered by the BIPAI, the COE offers care to adults through a family clinic at the COE, which has 120 adults in active care. It also runs a teen clinic one Saturday a month, which has about 100 teenagers who patronize this clinic for clinical care in the morning, followed by activities that promote their educational and psychosocial development. Aside from working with the partners, the Malawi Ministry of Health also supported the CDC, Baylor School of Medicine and Howard University efforts.

“With support from UNICEF and others, we were able to help purchase lab equipment and supplies, train nurses and lab technicians, and provide private courier services to transport the samples from health facilities to the labs for DNA PCR testing,” says Reuben Mwenda, deputy director, health technical support services-diagnostics, Malawi Ministry of Health.

Malawi’s Challenges and Critical Issues

UNAIDS states the HIV response in Africa is at a turning point, with countries in East Africa reporting good results due to access to testing and treatment. In Malawi, signs of positive change are evident.

Malawi’s AIDS response has stabilized the HIV infection rates. However, UNAIDS warns that more resolute interventions in the areas of finance, community empowerment and political drive are necessary to increase the effectiveness and reach of HIV prevention, treatment and care.



DNA PCR laboratory at Kamuzu Central Hospital lab in Lilongwe, Malawi

For several years, the CDC-GAP and its partners have provided assistance — technical guidance, resources, training and direct linkage to care and treatment — to strengthen Malawi’s laboratory capacity to test for HIV and monitor diseases. In 2002, Howard University received a \$5 million grant from CDC-GAP to provide technical assistance to support and strengthen laboratories and train lab staff and faculty from the lab training programs at the local colleges and universities. In 2006, the Ministry of Health in Malawi awarded a \$280,000 subcontract to HUTAP to hire lab managers and an epidemiologist for the National HIV Reference Laboratory and to roll out rapid HIV with western blot and CD4 testing training.

“Since 2003, Howard University has worked closely with the Malawi Ministry of Health and the other partners and collaborators to progressively strengthen and broaden HIV testing and training capacity and build a sustainable national laboratory infrastructure with the capacity to meet both the country’s strategic plan for health care delivery and its response to HIV/AIDS,” Porter says.

To accomplish the scale-up of laboratory services, the coordination and involvement of partners has been critical in key areas:

- Consultative meetings with stakeholders
- Development of policies and strategic plans
- Coordination with district health officers and administrators
- Identification of funds to support activities

Challenges, though, have surfaced as in the building of this much-needed laboratory infrastructure. It has been especially hard with limited and inconsistent procurement systems for ordering lab reagents and supplies, staff shortages that often hinder the motivation of the existing staff, and few experienced lab supervisors and managers, admits HUTAP’s Porter. To overcome these obstacles, HUTAP, the Malawi Ministry of Health and other key stakeholders are coordinating activities that provide critical data — assessments, site visits and other programs — that highlight gaps in the system and help them decide where to provide the technical and structural support.

One example involves a strategic mentorship program that HUTAP introduced to improve the quality of laboratory supervision in Malawi. Mentors are hired by HUTAP as lab supervisors or coordinators to work side by side with the laboratory supervisor on quality control, documentation/recordkeeping, communication, equipment maintenance and stockkeeping. Since 2008, the mentorship program has effectively helped new lab technicians to understand and partake in supervisory roles and responsibilities. It also has provided essential knowledge that has enabled laboratory staff to implement good clinical laboratory practices, improve documentation and recordkeeping, enroll and monitor quality assurance procedures, and enforce corrective action to remedy deficiencies.

Other problems facing Malawi involve the critical shortage of experienced laboratory personnel. Porter says HUTAP is collaborating with the Ministry of Health to strategically place staff, as they return to the workforce, in laboratories where the demand for testing services is high and where good supervision is essential for quality services. HUTAP also will recruit senior-level and experienced laboratory personnel for the next couple years to continue raising the standards of laboratory testing and training.

“Howard University is addressing lab staff shortage by hiring people from the private sector and Southern African Development Community region on behalf of the Ministry of Health,” Porter says. “These hires have the right skill set to help mentor new staff members.”

The Ministry of Health is trying to address the experience shortage with a mandate to increase the number of lab professionals who graduate from Malawi colleges every year.

“We’ve introduced a bachelor’s degree lab program, and we’re encouraging those who have pursued master’s degrees to return and use a higher quality of skills in Malawi,” says Mwenda. “We’ve also updated lab facilities, funded automation projects, and bought new equipment, supplies and services so there is no interruption of services.”

The Work Continues

Today, HUTAP is working with a new, five-year \$2.5 million cooperative agreement signed in 2007 by CDC-GAP for building laboratory capacity through preservice and in-service training. This will be done by providing in-service and preservice training for laboratory technicians, supervisors and medical laboratory science students; establishing laboratory centers of excellence in HIV-related testing; strengthening the laboratory science curriculum; improving teaching capability at the training institution; addressing human resource shortages through the provision of technical and managerial staff; and developing a national quality-assurance system for HIV, CD4, PCR and routine laboratory testing.

“Over the past year, HUTAP felt the critical need was to train laboratory technicians from the central and district hospitals in CD4 testing and DNA PCR due to the rapid PMTCT and ART [antiretroviral therapy] acceleration plans, as well as the implementation of EID [electronic identification device] services,” Porter said. “Now, under this new initiative, we intend to build this laboratory capacity with lab tutors who are oriented in this area and students who have received the necessary training at service delivery sites throughout Malawi.”

By David Perilstein



Standardizing Solutions to Change the Face of Laboratory Services in Tanzania



Lessons Learned:

- *The input of local and national level governments is critical during the design and implementation phases.*
- *Standardization is essential to efficient contract management, construction, mentoring, training and supervision.*
- *Training via face-to-face mentoring accelerates the pace of change.*
- *Receiving donations of used equipment is not the answer to building sustainable capacity in a new laboratory; a supply of reagents, maintenance and training are necessary.*
- *Communication is key at all levels, and the frequency of communication needed is frequently underestimated.*



Patients at Mt. Meru laboratory before modernization.

In certain African countries such as Tanzania, lack of health care infrastructure impedes progress not only in controlling the HIV/AIDS epidemic but in the overall provision of health services. Even when sufficient stocks of medication are available, shortcomings with certain ancillary services, such as laboratory testing, contribute to the challenges of diagnosing and treating HIV/AIDS and other diseases.

Abbott, the global health care company, was compelled to action in the late 1990s as the HIV epidemic in Africa was worsening. In 2000, Abbott CEO Miles White saw firsthand the issues of crumbling infrastructure during his visit to Muhimbili National Hospital, Tanzania's most advanced medical institution and university medical center. Reflecting on the experience, Miles said "I learned more in 10 minutes at Muhimbili than I had in reading all the newspapers and reports."

It was evident that, in order to address HIV in Tanzania, health system deficiencies needed to be modernized. After the visit, a comprehensive plan was put in place to fight AIDS in Tanzania by first addressing the weak health system that resided at the top of the Tanzanian health infrastructure, Muhimbili National Hospital.

Abbott with the support of the government of Tanzania, began a program to systematically improve laboratory infrastructure and services. While the initiative is a work in progress, Abbott has obtained measurable improvements in both turnaround time and the quality of patient results.

"In 2007, the regional laboratories in Tanzania were devoid of automation, similar to where we were in the U.S. in the mid-'80s," says Larry Wood Jr., program manager for Abbott Fund Tanzania. Wood, who is in charge of implementation and training in the project, explains, "Although they are relying on manual methodologies in many cases, local laboratory staff can generate acceptable results."



Abbott employee volunteer working alongside Tanzanian lab worker.

AIDS and Other Conditions

While HIV affects the population at a rate of about 5.7 percent throughout the country, in some places the rate goes much higher, up to 12 percent in the Lake Victoria region, for instance. But non-HIV patients often bear the brunt of the laboratory inequities in Tanzania.

“When antiretroviral therapy became available for people with HIV, laboratory services in the region were very poor, because the outdated facilities were not equipped to deal with the influx of patients needing ongoing disease and drug monitoring. It was hard for any of these labs to provide adequate patient care, without proper equipment, reagents, training and technical expertise. A physician without laboratory results is treating the disease blindly, unable to definitively define the best course of treatment for the patient’s changing condition,” says Gloria Kulaya, M.D., M.P.H., technical manager for monitoring and evaluation for the Abbott Fund Tanzania.

Global AIDS agencies like PEPFAR and the Global Fund tried to improve the situation by funding the update of laboratories and tests performed specifically for HIV patients. “This improved services for those with HIV, which is its charter; however non-HIV

patients didn’t receive the full benefit from the rehabilitations. For example, if you were HIV-positive, you’d get your results back quickly; if not, you could wait at least a week for your results,” Kulaya says.

Abbott’s first major intervention was to rehabilitate Muhimbili’s 52,000-square-foot Central Pathology Laboratory, in which the laboratory staff struggled to keep up with the hospital’s workload using broken and outdated equipment. The Abbott Fund installed new chemistry, hematology and immunology instruments and stocked the lab with reagents. In addition, the laboratory, and eventually the entire hospital, was fully computerized. To address the challenge of maintaining and servicing instruments, two Abbott field service engineers were dedicated to the new laboratory. Abbott field service personnel have access to the requisite parts and training to ensure that instruments are available 24 hours a day, seven days a week. In addition, the company also provides a full-time technical adviser to work alongside the technicians and train them on the use of quality control, instrument maintenance, reagent procurement and general laboratory operations and management.

Abbott also funds non-Abbott instruments and reagents. Most recently, Abbott Fund purchased a highly technical molecular instrument to diagnose HIV in infants early enough (before 18

months) to effectively treat them before they are overcome by the disease. As a result of this significant investment in equipment, training and personnel, Muhimbili is one of the highest quality and most sophisticated laboratories in East Africa.

Creating Efficiencies Through Standardization

In 2007, with the experience of Muhimbili as a reference point, the government of Tanzania asked Abbott Fund to consider renovating each of its region's laboratories; Tanzania has 20 regions and three larger regional-level laboratories for a total of 23 laboratories that needed immediate attention. Abbott agreed and began working with the government to determine the implementation strategy.

Abbott Fund, a foundation funded solely by Abbott, visited each lab together with its lab designers, architects and designated government officials. The team makes a determination as to whether the laboratory can be renovated or requires demolition and completely new construction. Key to the strategy is the intent to deliver a standardized final laboratory.

Standardization is an important aspect of the project. "From the very beginning, we wanted to provide a standardized solution," says Christy Wistar, M.B.A., vice president of Abbott Fund Tanzania. "We wanted all 23 buildings to look and feel alike." That goal has been partially hindered by the fact that some of the projects are complete teardowns, while others are rehabilitations. Right now the ratio is running about 50/50, she says.

While each of the labs differs in small ways, the overall plan to provide a standardized design helps to maintain control of the process and costs. As part of the program, Abbott installs safety equipment to provide protection from infection and contamination of laboratory staff. "The bio-safety cabinets and fume hoods are an important component of our overall program. It's not only about better quality results but also better and safer working conditions for laboratory personnel," says Wood.

Prompt Quantification of Benefits

Of the 23 laboratories slated for renovation, eight are now complete, five are under construction, and 10 more labs are planned for 2010, according to Wistar. Each lab costs between \$400,000 and \$500,000 dollars, she adds, a little more than originally planned but not out of line considering inflation and an expected three-year project investment of \$10 million.

While many of the rehabilitated labs are just now coming on line, Abbott measured improvements at one lab, the trial project in Mt. Meru Hospital, Arusha, Tanzania. There, the number of tests performed rose from an average of 15,000 to 134,000 per year, while turnaround time decreased from an average of three to 14

days to less than 24 hours. The number of clients using laboratory facilities also rose, from an average of 5,000 to 38,000 per year.

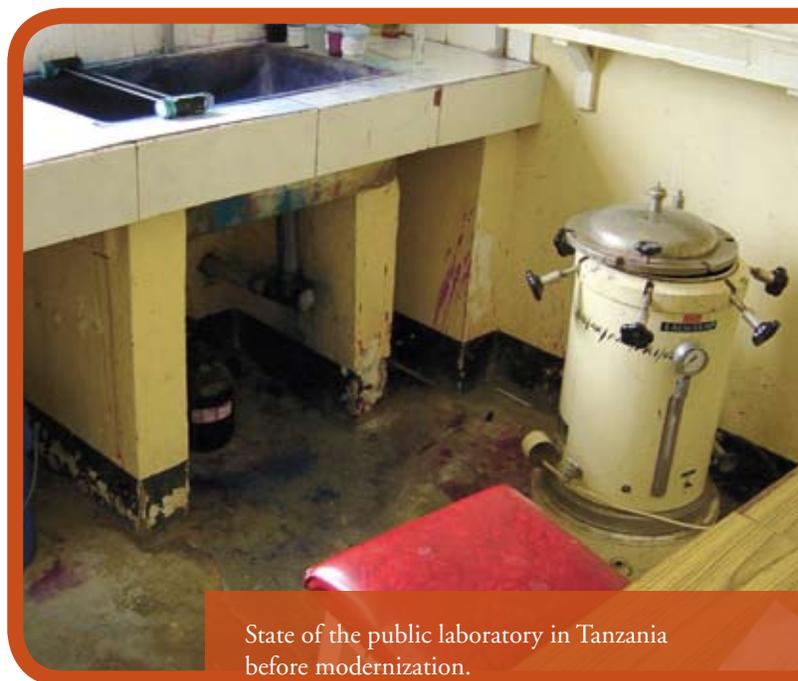
For some of the more recently completed labs, it is too early to measure results. Kulaya says they came up with a list of five indicators — among them the number of patients served, the number of test requests completed, instrument status, reagent inventory status, and turnaround time of results. The laboratories report back to Abbott Fund on Monday of every week. Currently, data collection is taking place manually because the monitoring system is not yet computerized.

Overcoming Logistical Difficulties

Even in the newly modernized laboratories, shortages of training, power or reagents sometimes mean that patient tests are not completed.

With the exception of Muhimbili, where Abbott supplied instruments for clinical chemistry, hematology and immunoassay, the Tanzania Ministry of Health is supplying laboratory equipment for the regional laboratories.

"One of the major challenges with the equipment purchased by the government is that until recently, no plans were made for service. Relatively new equipment can be inoperable for weeks or months because the local distributor is not a reliable source of service or parts. The problems are worse when equipment is donated without provision for local procurement of consumables or service.



State of the public laboratory in Tanzania before modernization.



Mt. Meru laboratory after modernization.

“Through our day-to-day contact with the laboratories we’ve found that, often due to a lack of reagents or hardware issues, relatively new analyzers are inoperable,” says Wood. “For example, we found an instrument where the hard drive had failed on the system after installation, and without a service plan in place, the staff put a blanket over the system and the associated tests were not performed for weeks. “I can’t tell you how critical qualified service and support are to the management of a modern laboratory,” says Wood.

As part of their training and implementation program, Abbott provides mentors to work with lab personnel side-by-side for two months during the start-up process to ensure the lab has good processes and procedures in place and is able to work through many on-site operational issues. Supervision of sites is also done weekly by e-mail, fax or telephone to ensure the sites are running, instruments are in good condition, and reagents and quality control are available.

However, by far the most difficult logistical problem facing labs in Tanzania is that of keeping reagents in supply. A reagent is a consumable resource used with the analyzer to produce the test result, like paper is to a printer. A busy laboratory requires hundreds of different reagents with different expiration dates, making laboratory inventory and procurement a huge logistical challenge in a country like Tanzania.

At Muhimbili, Abbott provides reagents and other consumables at no charge or they are purchased from local suppliers. Abbott support personnel are responsible for managing inventories and ordering supplies. In the regional labs, because it isn’t Abbott instrumentation, two local distributors as well as the government’s

own procurement agency, are responsible for supplying the country’s laboratory supplies.

The reagent ordering process has been a source of frustration for the laboratory staff in Tanzania. “The main thing is that it just takes too long, forms are filled out manually, requiring signatures and sent by mail to the Medical Stores Department, where there is a huge backlog of forms,” says Kulaya. In fact, often, reagents are shipped out to the laboratories without regard to need or inventory on site. It’s called a “push” system whereby reagents are pushed from the Medical Stores Department to the laboratories without an order. This inevitably ends with oversupply and storage issues for some supplies and running out of others.

Abbott is trying out a new method of ordering reagents at the labs, Wood says. “We’re trying to convert from a “push” system to the more traditional “pull” system where reagents are ordered as needed. Right now, we have a pilot program, and we should have feedback from that within the next six months,” he adds.

Ensuring the Future Through Education in the Lake Victoria Region

One of the regions hardest hit by the AIDS crisis, the Lake Victoria region in the north, with its population of 13 million, may also serve as another kind of laboratory for solving some of the country’s global health problems. In addition to building or renovating labs across Tanzania, Abbott is partnering with U.S.-based Touch Foundation Inc., to increase medical education. The Touch Foundation was working on the health care worker shortage in Tanzania and enlisted Abbott support, when Abbott was beginning the lab modernizations in the Lake Victoria region.

Every year, Abbott funds more than 100 scholarships for medical technologists, for a full three-year program, at (Weill) Bugando University College of Health Sciences in the Lakes region.

“Well-trained lab managers and medical technologists are the key to ensuring the future of these laboratories,” says Wistar. “We need to ensure that Tanzania has a next generation of qualified medical technologists. Beyond training laboratory staff to use the equipment or conduct tests and read results, Abbott’s mentoring program is instilling a new discipline. Through daily observation and a weekly phone questionnaire, we’re communicating that the role of the laboratory is vital to the health care system and it’s not acceptable to let patients and physicians down. We’ve established, most importantly, a new sense of accountability.”

By John Otrompke, J.D.

Christy Wistar contributed to this article.

Bringing Modern Medical Science to Mali



Lessons Learned:

- *Effective research partnerships require strong leadership and government support.*
- *A cooperative decision-making style enables the sharing of technical and cultural knowledge.*
- *Providing career opportunities and research grants in developing countries entices researchers to return to their home countries after obtaining their graduate education elsewhere.*
- *Collaborations that include sophisticated research projects and advanced training of local personnel can provide the foundation for a new, world-class research system in even the most resource-constrained countries.*



Guindo Oumar (left), lab manager, and Professor Anatole Toukara, scientific director, work together at the Center for HIV and TB Research Program (SEREFO) in Mali.

Mali, covering a vast wedge of sub-Saharan Africa, is one of the poorest nations in the world. Its health problems are multi-farious, with the country's four million annual cases of malaria representing a severe burden. Yet the situation is not hopeless. Mali is the scene of an international partnership that has created a world-class medical research center and, within it, the seeds of a research-based modern medical system.

Back in 1989, Robert Gwadz of the National Institute of Allergy and Infectious Diseases (NIAID), a component of the U.S. National Institutes of Health (NIH), was busy developing the “perfect mosquito” — a transgenic version of *Anopheles gambiae* in which the malaria parasite could not breed. The idea was to flood a local *Anopheles* mosquito population with the transgenic version and eliminate the malaria threat through interbreeding. But, Gwadz recalls, “We had no idea how to manage such a release.”

Gwadz contacted Yéya Touré, a Malian researcher with whom he had previously worked. He received Rockefeller Foundation and

World Health Organization (WHO) funding for the initial effort. Within two years, NIAID added its financial support and assigned entomologist Richard Sekai to coordinate the program inside Mali. Ogobara Duombo, a young Malian physician returning from his education in France, together with Louis Miller, then head of the Malaria Section at the NIAID Laboratory of Parasitic Diseases, extended the research agenda into malaria treatment. These efforts in 1992 became the Malaria Research and Training Center (MRTC) within the national medical school (now part of the University of Bamako).

Steve Smith, current director of the NIAID Office of Global Research, says that the project's success was initially due to the “strong commitment in NIAID and Mali by certain individuals. You can't do a project like this unless there are talented researchers with a mix of skills including science diplomacy.” Smith also notes that the Mali government's consistent support has been crucial. “It is a real partner,” he says. “Other countries don't have this piece.” Pressed by the popular demand for malaria control measures, the Mali Ministry of Health supported the MRTC's creation at the nation's public university. It now works with MRTC researchers



Photo provided by NIAID.

on joint projects. These include evaluation of mosquito control measures, malaria drug resistance and the training of laboratory technicians.

At first, the biggest problem was a lack of local resources. For example Gwadz found that, after a fuse blew in one of the original labs, there were no fuses for sale in the entire country. He had to bring a suitcase full back from Paris. “There were no supplies, no basic laboratory chemicals. Everything had to be ordered from abroad,” he says. Electrical power was another serious problem, with daily outages when dams were low at the start of the rainy season.

These problems were largely resolved through the construction of new research and training facilities, which NIAID funded over the years. The development of reliable supply chains helped as well. The MRTC now boasts of seven fully equipped laboratory and office buildings in Bamako plus several field research sites, all equipped with emergency generators. Communications are assured by satellite dishes providing a direct Internet link to the NIAID computer network in Bethesda, Md. Most important is the laboratory equipment. “In some countries, we have to bring everything we need. This is not the case in Mali. We can do flow cytometry, PCR [polymerase chain reaction] and other advanced techniques,” says NIAID researcher Amy Klion. International research groups from other organizations now regularly make use of the MRTC facilities.

Expansion to Other Diseases

Klion is an expert in filariasis, an infection of parasitic worms. The lymphatic form of the disease, which is common in Mali, causes

severe swelling and ultimately elephantiasis. Lymphatic filariasis is transmitted by the same *Anopheles* mosquitoes that transmit malaria, leading to many coinfections.

The fact that Klion is working with the Mali project is indicative of how it has expanded. Klion relates, “One of Yéya Touré’s students, Yaya Coulibaly, came to work at NIAID. He was interested in filariasis, and that was the start of our collaboration.” The filariasis project led to a series of investigations on insect-borne diseases, among them leishmaniasis.

In 2002, the MRTC and the Entomology Unit of the University of Bamako medical school jointly formed a NIAID-sponsored International Center for Excellence in Research (ICER). NIAID designed the ICER program based on its experience with the MRTC. One of the ICER program’s goals is to create locally managed, sustainable research and training programs that build indigenous infectious disease research capacity and address shared scientific priorities. The main concern is diseases of local importance. (NIAID also formed ICERs in Uganda and India.)

An HIV/tuberculosis unit became a third part of the Mali ICER in 2002. The focus on HIV grew out of a proposal from the medical faculty dean. HIV prevalence in Mali is relatively low (about 1.5 percent in people 15 to 49), but TB is much more common. It, therefore, made scientific sense to include a concentration on HIV/TB coinfection. Gwadz notes, “Mali is also safe, cooperative and politically stable. The HIV/TB unit has proved a successful program.”

The increasing complexity of the Mali scientific program brought with it additional organizational complexity. NIAID now maintains two senior science administrators at its Mali office. Since 2004, a five-person Mali Service Center, run for now by outside contractors, provides accounting services for the researchers in Mali.

Decision-Making Process

The Mali staff has the status of a NIAID contractor; it is not an outside grantee. As contractors, staff members are paid directly by NIAID within the scope of specific research projects. The Americans and Malian consult on study designs, with Malians the primary executors. The American collaborators visit as needed. “I go to Mali every three months, when the data monitors go, and also to teach techniques such as PCR,” says Klion.

Of course, the U.S. researchers have a more America-centric view of the process than the Malians. “We have an idea, for example,

about mosquito mating behavior, and the Malians figure out the details based on their local knowledge,” says Gwadz.

But for the Malian researchers, “Almost the entire study is done in Mali, including the lab work,” says Anatole Tounkara, present dean of the medical faculty and director of the HIV/TB research program. “It is a great thing for us that the NIAID considers us on the same level. This is not NIAID science but our science.”

Often the Malian scientists help determine research direction. Seydou Doumbia, deputy director of the MRTC entomology program, cites the example of leishmaniasis. “One of our colleagues was looking at leishmaniasis, but the NIAID people said that there was no leishmaniasis here. So we said here are the data. And they said, great, let’s see if we can do our vaccine study in Mali.” The HIV/TB program has formalized this process with a joint Mali-U.S. scientific review committee that approves research proposals from both countries. Once fully developed, all ICER protocols must receive final approval by Malian and NIAID Institutional Review Boards to ensure that protocols meet international standards.

Decisions cannot go in one direction because the Malians are the ones who have to cope with the local conditions. Hammering out an experimental protocol is, therefore, an iterative process. The NIAID scientists may propose a specific research idea, but the Malian scientists refine it according to local conditions. As Sekou Traoré, co-director of the MRTC recounts, “They [NIAID] say what they want to do, but we can say it is not feasible. We can say no at the initial phase, but when we have elaborated a protocol together, turning it down is no longer an option.”

Rick Fairhurst of NIAID’s Laboratory of Malaria and Vector Research illustrates the way the cooperation may evolve. His study relating human genetic mutations to malaria severity in 1,200 Malian children is yielding a treasure trove of data. Fairhurst is investigating the action of human mutations known to provide some protection. His Malian co-investigator, Mahamadou Diakité, is combing the same data set to find previously unrecognized protective mutations.

Further adjustments in research protocols occur at the village level, where studies are carried out. The Malian investigators first hold a meeting with the local chiefs, seeking their buy-in. These meetings are not pro forma as the chiefs usually ask very pointed questions. Once the chiefs have approved, the investigators call a villagewide meeting to explain the research. “We may have to alter the protocol based on what the villagers say,” notes Klion.

Villagers obtain concrete health benefits while participating in a study. They may receive health care that addresses the disease or

coinfection under study. Enhanced treatment for other diseases detected in the course of the study is another possibility. These services are provided either by the study personnel or nearby public clinics. There are also other types of limited assistance: Klion tells of a clinical trial in which participants received free breakfast because the study drug had to be taken with food. When the trial was over, the participants requested extending the free breakfasts for another month until harvest time. “But we were unable to do that,” recalls Klion. “It was heartbreaking.”

Creating a New National Scientific Enterprise

A critical component of the NIAID-Mali partnership is training and education. This too is a two-way process. On the one hand, Malians learn about conducting advanced research. On the other, NIAID scientists receive an introduction to on-the-ground tropical medicine research.

The training programs are multi-faceted. There is a constant exchange between Mali and NIAID. In some cases, it is more efficient to send people back to the United States than train them in Mali. Malians in the United States can work side by side with the personnel employing advanced techniques. Later, their U.S. mentors visit Mali to see how trainees are doing. These visitors may help adapt NIAID practices to Malian circumstances.

The ICER also organizes educational workshops held within Mali. These cover subjects requiring broad and rapid dissemination, such as good clinical and laboratory practices or ethical trial conduct. Other short courses have included subjects such as basic immunology and grant writing.

NIAID has sponsored American postdoctoral and predoctoral fellows who go to Mali to gain experience under field conditions. For five years, the program benefited from a grant supporting Americans from minority groups who concentrate on tropical medicine. About 20 grantees worked at Mali ICER research sites for up to eight months.

Conversely, Malian medical school graduates have received funding — from the NIH, WHO or the hosting universities themselves — to pursue advanced degrees in the United States or Europe. These students typically go to schools where faculty members have an interest in pursuing the type of research that the students have worked on in Mali. Unfortunately, this support has been increasingly difficult to obtain.

Seydou Doumbia followed one such professional path. After graduation from the national medical school, Doumbia worked at the MRTC during the early nineties, collecting and analyzing epidemiologic data on malaria. In 1994, the MRTC received a WHO

grant to sponsor overseas study for promising doctoral candidates. Doumbia benefited from that grant and from an NIH fellowship to learn English while working at Johns Hopkins University. He resided in the United States for seven years in all, receiving his doctorate from Tulane University in New Orleans. The malaria research program rehired him as a lead scientist when he returned to Mali. He is now also a professor of epidemiology in the University of Bamako Department of Public Health.

Doumbia's story illustrates several important strengths of the MRTC and ICER partnerships. The first is retention. Local scientists who receive international training return to Mali to continue their careers. The collaboration with NIAID provides a sophisticated scientific milieu in which the young researchers can practice what they have learned. "NIAID helps reinforce human capacity," says Doumbia. "Its support makes it possible for researchers to come back to work in the country."

An overarching benefit is that the returning scholars are able to take up teaching positions within the medical school. As of 2009, there were about 5,600 medical students enrolled at the University of Bamako, double the number 10 years ago. The faculty is stretched very thin. Tounkara, the medical school dean, has high hopes for the returnees. He says, "If you have the human resources, naturally they will educate other people, giving back what they have absorbed."

Lastly, the researchers' international education makes them familiar with modern scientific operations. These researchers' presence in Mali ensures the stability of the scientific enterprise there. This is particularly true because they have learned how to obtain independent research grants from foreign funders. In this way, returning science graduates form the core of a growing self-sufficient research enterprise.

Next Steps

The Malian staff at Mali ICER now amounts to some 160 investigators, technicians and support staff. The original malaria project started out looking at mosquito behavior and control then expanded into epidemiology, treatment and vaccines. From 2006 to 2009, the MRTC/ICER initiated 39 human malaria studies. Fifteen involve malaria vaccines and the rest range from human protective factors to various drug regimens. There is also a study looking at the immunology of filaria-malaria coinfection. Other recent filariasis investigations include two treatment trials. The HIV-TB unit meanwhile is conducting a long-term study of immune responses to TB, with and without HIV coinfection. It is now enrolling trials looking at HIV treatment response. Among the projects at earlier stages of development are research on leishmaniasis (an epidemiologic study possibly leading to a vaccine trial) and the tick-borne disease, relapsing fever.

Future directions include more involvement with national development. To relieve overcrowding at the University of Bamako, there are ongoing discussions about building a second national university. This would require significant expansion of the current faculty, and the ICER has a role to play here. "There is only one university in Mali, and I hope that we can generate more high-quality researchers able to teach in new universities as we open them...This is my vision," says Tounkara.

Malian researchers also mention their interest in further emphasizing "translational research." This research would show how to apply scientific findings to improve community health. For example, it is not enough to discover a potent malaria treatment if it rapidly succumbs to drug resistance when put into clinical practice. Translational research would find ways of administering the drug that retain its efficacy. MRTC's Traoré says, "We have to strike a balance between current research and what would be useful to the public in future. We want to be part of a new generation of scientists that uses new technology to respond to people's needs."

Traoré himself is back working on the original research concept, the genetically engineered malaria-proof mosquito. New gene manipulation techniques make the idea more promising, and Traoré received an independent grant from the University of Kiel (Germany) to further develop this mosquito.

The NIAID researchers welcome a move toward such independent research, which is a major goal of the collaboration. NIAID's Klion, who first worked in Mali during the late 1980s, notes that the Malian education system historically has not encouraged self-directed activity among its graduates. But, she says, "There has been a huge change in recent years. The Malians have more skills and autonomy, with the malaria group furthest along in becoming more independent."

The Mali experience underscores the benefits from an international research collaboration based on mutual respect, common scientific objectives and shared responsibilities. The ICER is advancing to the point where its achievements will feed on themselves, setting the stage for further progress. The question remains as to the ultimate health, economic and cultural benefits for the country as a whole. These depend on Mali's ability to apply what its scientists have learned. Mali faces a desperate lack of resources, but the intellectual vitality of its nascent scientific establishment promises to bring the country into the 21st century.

By David Gilden

Freedom of Breath, Foundation of Life: China's Neonatal Resuscitation Program



Lessons Learned:

- *Government support lends credibility and urgency to the implementation of health programs.*
- *Medical organizations can help build awareness and support for programs and set a foundation for scale-up opportunities.*
- *Once a critical program goal is met, it is essential to work on sustainability issues and building long-lasting enthusiasm for future growth.*



The large mannequin has an anatomic respiratory system.

Birth asphyxia is the No. 1 cause of infant mortality in Chinese cities and the No. 2 cause of mortality of children less than five years old nationwide. Birth asphyxia occurs before, during or just after birth, when a baby is deprived of oxygen.

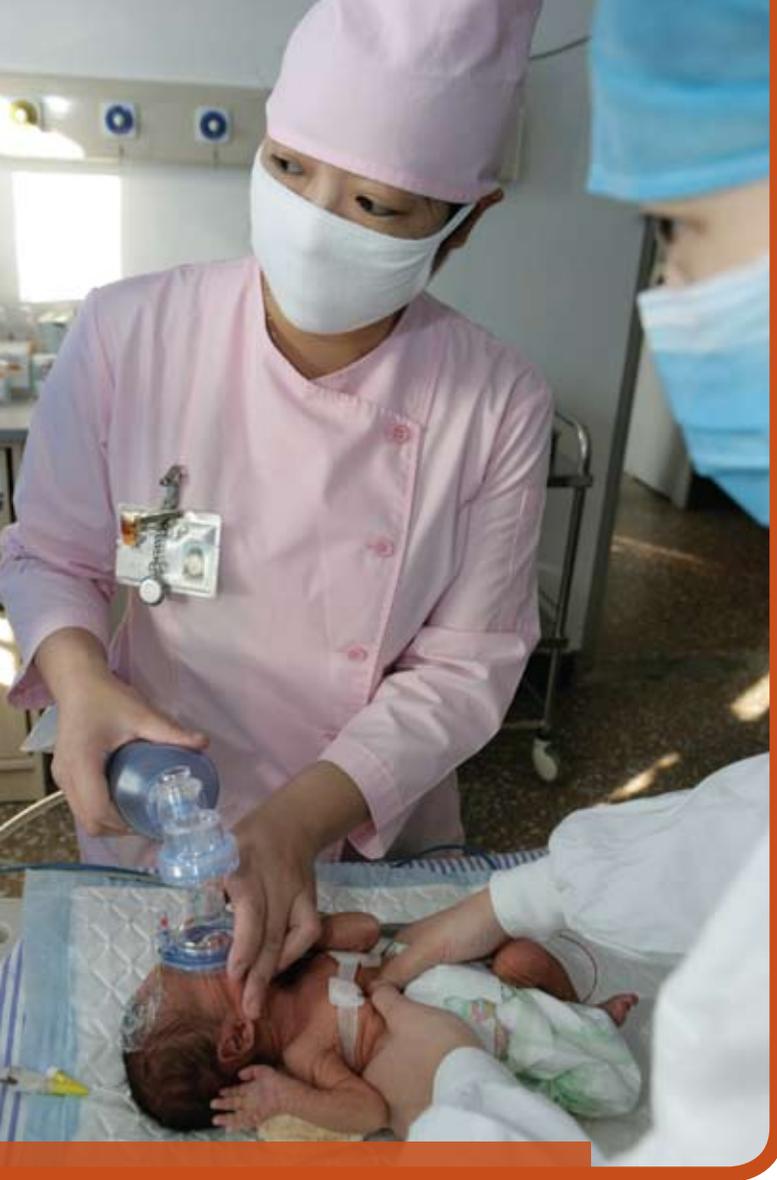
An estimated 17 million live births occur in China each year, nearly four times the amount in the United States. In 2002, infant mortality rates were documented at 29.2 per 1,000 live births, and 20.5 percent of infant deaths were attributed to birth asphyxia.

Though previous collaborative efforts attempted to bring lifesaving technology to select regions of China, the Freedom of Breath, Foundation of Life multi-sector partnership was the first to successfully implement the China Neonatal Resuscitation Program (NRP) in a systematic and sustainable way across the country through governmental, professional and private enterprise collaboration.

“AAP [American Academy of Pediatrics] representatives worked for a number of years with some local Chinese agencies but were unable to attract interest beyond specific work environments and certainly not able to effectively discuss a public health commitment to neonatal resuscitation,” says William Keenan, Ph.D.

In 1987, the AAP, a not-for-profit professional organization of pediatricians, conducted the first course in the NRP in China. Efforts to establish the NRP as a national protocol failed through 2001, when AAP hosted a luncheon meeting in Beijing with some provincial leaders and Chinese Ministry of Health (MOH) representatives. Enthusiasm remained low. In response, then-executive director of AAP, Errol Alden, M.D., and Keenan contacted Joy Marini at Johnson & Johnson Pediatric Institute LLC (JJPI), and suggested they pursue an established NRP in China.

JJPI, a part of Johnson & Johnson Corporate Contributions, is committed to saving and improving the lives of mothers and babies. JJPI’s Marini met with Zhang Deying and Yang Qing of the



A baby receives resuscitation in a neonatal intensive care unit.

MOH in 2002 to discuss how the private institute and government could partner to address birth asphyxia.

The Freedom of Breath, Foundation of Life program was developed to reduce infant mortality and morbidity by ensuring there is at least one person trained and skilled in neonatal resuscitation at every hospital delivery. Additionally, plans included establishing an NRP training program at every hospital that provides obstetric services.

To establish this program and implement NRP across the nation, the partnership required not only governmental and financial support, but technical expertise and the cooperation of health professionals who would be trained and eventually would train others. The MOH appointed the National Center for Women and Children's Health (NCWCH), a government organization under the Chinese Center for Disease Control, as the implementing organization for the program.

The NCWCH provides technical support to the MOH on policies affecting the health of Chinese women and children. The center also has had previous experience implementing, monitoring and partnering with international organizations to create national programming.

With a program leader in place, the partnership sought the technical expertise of AAP, which, along with the American Heart Association, developed an internationally established NRP educational program. This gold standard program has been taught in more than 60 countries and was the preferred method for educating health practitioners in China.

The AAP worked closely with Chinese medical professional associations to form the partnership's technical team. The Chinese Society of Perinatal Medicine (CSPM), a professional organization of obstetricians and neonatologists, was an obvious fit for this partnership. Members of the society are at the center of neonatal resuscitation in Chinese hospitals, and a part of the group's mission is to provide continuing education to members. Past experience with NRP training in China also made them a valuable partner.

The Chinese Nursing Association (CNA), a nonprofit professional organization for nurses, takes a lead role in providing nurses' professional education. By including this group, the partnership recognized the important role of nurses in neonatal care and resuscitation. CNA brought the idea to train midwives, who traditionally do not receive formal training in resuscitation skills, in addition to nurses, to ensure a skilled person is present at every delivery.

With partners in place, a task force was formed to oversee strategy and implementation of the program. The Freedom of Breath, Foundation of Life initiative was an educational intervention, based on an established NRP, in targeted provinces. Eventually, the program would reach a national scale.

Setting the Foundation

In the United States and other countries, medical societies have mature structures and are capable of spearheading national programs and recommending health protocols in their field. However, because of China's political structure, Chinese medical societies do not have the same administrative power and personnel. Working closely with the AAP, the Chinese Society of Perinatal Medicine drafted guidelines for the MOH to establish a national NRP policy.

CSPM and AAP also collaborated to translate AAP training to fit Chinese context. Twenty-one national health care providers, trained by AAP, were responsible for providing technical support in each of

Building a Sustainable NRP in China

To maintain practitioners' enthusiasm and continue growing the program, the implementation plan includes a public relations campaign and incentives for participants.

A biannual convention is held to reward notable practitioners and provinces with exceptional training and program implementation. Since it takes time to learn a skill and apply knowledge, it is important to build providers' confidence.

The convention not only encourages practitioners; it also provides a platform to discuss program development. Facilitating communication among participants and reorganizing the program to accommodate best practices were vital steps to ensuring participants' morale.

In addition to the convention and administrative and technical teams in each province, an interactive Web site offers another way to connect. Maintained by the NCWCH, the Web site provides access to training documents and updates, acts as a platform for knowledge exchange and allows instructors to submit training reports and other information.



Practitioners check neonatal resuscitation program equipment in an operating room.

The format of best-practice competition and sharing was unique for medical training programs in China and was met with extreme enthusiasm by participants. This model has already been and will be replicated in other MOH programs.

Moving Training Into the Hospital Setting

To maintain an NRP and ensure skills are properly implemented in hospitals, a hospital-based instructor program was piloted in nine select hospitals. This pilot program, launched in October 2008, encourages the cascading model of training and ensures a team of qualified instructors are present at each hospital. The pilot program also works to incorporate NRP in hospital management and establish neonatal resuscitation in case audits and review.

While a final report of the pilot program is under way, preliminary findings show that hospital-based instructors help institutionalize NRP at a hospital level, neonatal resuscitation inclusion in audits helps reinforce NRP knowledge and skills and helps identify steps to be strengthened, and a hospital-based staff builds teamwork among obstetric and pediatric staff.

Future plans include building long-term, sustainable NRP through hospital-based instructor programs, implementing NRP at township health care clinics and addressing skill maintenance and renewal. It is hoped that NRP skills will eventually be required for licensed obstetric service providers. The CSPM, CNA and the Chinese Society of Obstetrics are already advocating for this policy, and the MOH and its provincial bureaus are spearheading this effort.

Positive results of the program are already evident in the improved rate of birth asphyxia deaths. Providers are appreciative of the knowledge the program has brought their institutions. They believe their skills — and their confidence — have increased. Hospitals have gained technology. More babies are surviving, and midwives have the opportunity to pursue more specialized training.

Liu Jia, a nurse at Beijing Obstetrics Gynecology Hospital, completed NRP training herself and benefited from the technology during the birth of her son, Yang Yang.

“Every smile, every laugh, even every cry, is precious,” she says of her son, who is about two years old now. “Yang Yang is the future of our family. We’re so thankful for the trained team that knew exactly what to do when he was born and did not breathe.”

“The program is saving lives and improving the health of women and children,” says Tao Xu of NCWCH. “When I get frustrated, I take a step back and look at the big picture. That keeps me going.”

A Multi-Disciplinary Partnership

The Freedom of Breath, Foundation of Life program succeeds today due to the hard work and dedication invested by all partners — governmental, corporate and nonprofit.

Cultural differences posed a challenge to partners. Cooperation between Chinese and American medical teams was tested when developing the Chinese version of AAP training materials. The Chinese team was not familiar with copyright protocols and guidelines for intellectual property ownership, but with compromises from both sides, materials were created and distributed.

Additionally, communication methods required compromise. Initially the Chinese medical team did not understand the benefit of both external communications, through the media, and internal communications, through health practitioners, as a means to spread the program's message. In time, and after seeing some success, the Chinese team recognized that motivating practitioners and provincial bureaus via both modes could speed capacity building.

An ongoing challenge to the program has been securing adequate amounts of equipment sets, which can contain more than 40 items. Both national and provincial MOHs have provided equipment, and some hospitals have purchased sets. Still, with such a high demand for training, equipment can be hard to come by. The implementation team addressed this challenge by developing an equipment-sharing program early on. As training became more widespread, the lending system became better known by providers and hospitals.

Each year, teams of professionals from the CSPM and the CNA, led by NCWCH, visit hospitals to review implementation of the program and supervise training. NCWCH staff is responsible for evaluating the implementation of the program. Representatives interview health administrators and practitioners and review supporting hospital documents. Likewise, the CSPM and the CNA evaluate skill and knowledge advancement of hospital staff as well as equipment and drug checks.



Baseline evaluation at a township clinic

This long-term partnership relies on each of its member organizations to fulfill a vital role in the successful NRP in China. In addition to electronic communication and informal meetings between technical partners, full partner meetings are held twice a year to discuss and review annual implementation plans and related activities. Partners also discuss challenges, changes and ideas for future development.

Collaborators recognize the importance of respecting one another's expertise and working together with a clear goal in mind: that quality resuscitation and early newborn care be available to every baby born in China.

By Ashley Mastandrea



**“If you want to go fast, go alone.
If you want to go far, go together.”**

(African proverb)

The stories presented in the Case Studies for Global Health provide an inside look at the ways in which partners have addressed the complex challenges of developing and delivering effective health care for the developing world. They illustrate the ways various stakeholders — private funders, world health agencies, academics, pharmaceutical and biotechnology companies, public-private partnerships, and governments — have come together for a common purpose.

Some are success stories. Some are not. Most are works in progress. But in every case, these are frank and honest assessments of what was learned along the way.