# HealthTech IV

Cooperative Agreement #GPH-A-00-01-00005-00

Semiannual Report
April 2006 – September 2006

Submitted to:
United States Agency for International Development (USAID)

Submitted by:
Program for Appropriate Technology in Health (PATH)
1455 NW Leary Way
Seattle, WA 98107

USAID FROM THE AMERICAN PEOPLE

PATH A catalyst for global health

# Table of contents

## Executive summary

During the past six months, HealthTech has continued to make progress on all 14 subprojects as described in the report. We have conducted only preliminary work on three more: chlorhexidine commercialization and use in prevention of neonatal infection, zinc production and supply, and optimization of low-cost methods for determining the bacteriological quality of drinking water. As of October 10, we have now received the funding for these projects, so product development and/or product introduction plans on these three activities are now being drafted, and work will officially begin. Our progress on those three projects is not included in this report.

One issue that we will need to deal with in the coming months is the end of the Affordable Technologies for Health program, which has been a significant source of co-funding for the HealthTech program for the past seven years. The Bill & Melinda Gates Foundation has decided not to renew a grant with PATH for this "portfolio management" approach but rather to put out competitive solicitations of specific technology-related projects as needed. As a result of this and the SO-approach to funding HealthTech by specific project and objective, we now have limited ability to support "skunkworks" efforts. "Skunkworks" is our term for the early investigation of ideas for technology solutions to identify health needs in low-resource settings. This has been a cornerstone of our product development in the past and ability to envision and evaluate technologies ahead of the recognized need. We are seeking other funders for this purpose but would welcome more opportunities to discuss this limitation with USAID.

## Highlights and milestones of HealthTech projects during the past six months

- A synthesis of the research and program evidence presented at the Global Consultation on the Female Condom, held in September 2005, has been published and disseminated broadly in a May 2006 issue of PATH's reproductive health publication, Outlook. Participants at the meeting generally agreed that the potential for increased use of the female condom and its positive impact on health through prevention of sexually transmitted infections and pregnancy is substantial.
- Results from the formal stability study of oxytocin packaged in the Uniject™* device at BIOL, our private-sector collaborator in Argentina, continue to be promising. Drug potency remains within the allowable range and pH levels are steady.
- HealthTech and UNICEF cosponsored a cold chain workshop in Panama. Expanded Programme on Immunization and cold chain managers from 14 Latin American countries learned new approaches to cold chain strengthening and improving immunization access. The workshop was very well received.
- PATH's training manual on sharps waste management, developed under HealthTech and the Making Medical Injections Safer (MMIS) project, continues to be disseminated and translated in countries. The manual has been posted on both WHO's safe injection and PATH's websites.
- In Kenya, HealthTech helped the MMIS project develop a new low-cost needle pit design. The new approach, using a buried plastic barrel to speed installation and reduce costs, is being introduced in Kenya health care facilities.
- Results from the formal stability study of gentamicin packaged in the Uniject device at BIOL also continue to be promising. Drug potency remains within the allowable range and pH levels are steady.
- A global inventory of available neonatal resuscitation devices has been completed; a compendium of details of over 100 identified devices was produced in June 2006 and has been posted to the PATH website for public reference. The information should be very useful for program managers making decisions about purchasing devices for use in their neonatal programs.
- Validation results from a study of retinol binding protein/enzyme immunoassay (RBP/EIA) in Cambodia were published in a refereed journal: Hix J, Rasca P, Morgan J, Denna S, Panagides D, Tam M, and Shankar A. "Validation of a rapid enzyme immunoassay for the quantitation of retinol binding protein to assess vitamin A status within populations." European Journal of Clinical Nutrition advance online publication, May 31, 2006.
- A large evaluation (N=1,840) of the chlamydia immunochromatographic strip (CT ICS) test among high-risk women in four cities in Bolivia has been completed. This evaluation involved comparing syndromic management, the CT ICS test, ELISA, and polymerase chain reaction for determining CT status. Data analysis is underway, but initial results show that the performance of our test was poor (less than 50 percent sensitive). We will be evaluating the results further to determine how the test can be improved.
- HealthTech has developed a prototype system for purification of CD4+ cells from whole blood which uses commercially available magnetic beads and reagents. We have simplified this system and hope to improve its performance in the coming months. It will be used in conjunction with the detection system.
- The Kenya pilot introduction of the nevirapine (NVP) infant-dose pouch was completed and preliminary results have been written up and disseminated. Approximately 540 pouched doses of

* Uniject is a trademark of BD.

NVP syrup in Exacta-Med®† dispensers were provided to HIV-positive pregnant women by health workers in facilities in advance of giving birth. The pilot results showed high acceptability of the approach among the women and the providers. A summary of the results has been sent to USAID under separate cover.

- In September 2006, a prevention of maternal to child transmission stakeholders meeting was held in Kenya with more than 70 participants representing every province within the country and many of the partners. HealthTech presented the findings from the pilot introduction of the NVP infant dose package and discussed next steps for broader introduction of the take-home approach.
- A sourcing manual for the NVP pouch to facilitate procurement of pouches has been prepared and published on the PATH website.
- HealthTech has signed a collaboration agreement with Sequella Inc., a commercial company that has developed a promising transdermal patch test for detection of active tuberculosis (TB) disease. Early evaluations of the test in the Philippines and South Africa by Sequella show high sensitivity (greater than 85 percent) and specificity (greater than 92 percent) when compared to gold standard culture results. We are initiating dose-finding and performance evaluation studies in Ukraine in the coming months, working with the PATH staff and several local TB clinics in Kiev and Donetsk.

† Exacta-Med is a registered trademark of Baxa Corporation.

# Strategic Objective 1

# Publication of results of the Global Consultation on Female Condoms

## Goal of project

A key goal of the plan of action from the Global Consultation on Female Condoms is to build support from donors, policymakers, and women's health advocates worldwide to make the case for immediate, widespread promotion and distribution of female condoms as an important way to protect women, men, families, and communities around the world. USAID supported HealthTech to publish and disseminate the results of the consultation as a means of doing so.

## Status of project as of September 2006

The project is now completed with the publication of a synthesis of the research and program evidence presented at the Global Consultation on the Female Condom, held in September 2005, in a May 2006 issue of PATH's reproductive health publication, *Outlook*.

## Achievements and progress in the past six months

- Synthesis and analysis of the consultation was carried out and the publication completed. Over 100 experts from 15 countries gathered to discuss the current status and recommendations concerning the female condom. Participants at the meeting generally agreed that the potential for increased use of the female condom and its positive impact on health through prevention of sexually transmitted infections and pregnancy is substantial.
- Dissemination of this issue summarizing meeting findings and recommendations, relevant research, and the follow-up action plan ensures widespread access to the latest information on female condoms. It enhances the ability of policymakers and reproductive health program planners to develop effective strategies for female condom introduction. PATH printed and disseminated 14,000 copies to readers in 180 countries. Copies are also available at the following website: http://www.path.org/publications/pub.php?id=1266.

## Problems encountered and actions taken to resolve them

The original publication date was February 2006, but delays in the reviews and approvals pushed back the dissemination to May.

## Next steps and milestones expected in the next six months

This particular project has been completed, but HealthTech has recently received an obligation from the Office of Population and Reproductive Health to work on the advancement of female barriers. This includes some co-funding to find commercial partners for PATH's Woman's Condom, which has been developed with funding from USAID under the Contraceptive Research and Development (CONRAD) program. HealthTech will also be doing preliminary investigation of the use of the SILCS Diaphragm as a microbicides delivery device. The SILCS device was also developed with support from CONRAD. Work plans for these two projects are being drafted.

# Introduction of injectable contraceptive in the Uniject device

## Goal of project

The goal of the project is to increase the safety, acceptance, and reach of depot medroxyprogesterone acetate (DMPA) injectable contraceptives in the Uniject™[‡] device for family planning programs. Such products facilitate innovative new options, such as home injection of contraceptives and applications related to outreach.

## Status of project as of September 2006

In December 2005 Pfizer obtained internal management approval to invest in major scale-up and production of DepoProvera SC in Uniject to serve international donor markets, subject to final agreement with BD on a long term exclusivity and supply agreement for Uniject from BD to Pfizer. PATH continues to interact with Pfizer, BD, and USAID to facilitate progress.

## Achievements and progress in the past six months

Pfizer and BD were still negotiating terms of their exclusivity and supply agreement as of the end of this semiannual reporting period.

## Problems encountered and actions taken to resolve them

While numerous issues have been resolved they still have not closed the deal. Pfizer states it will not initiate any major investments in scale-up until the agreement is finalized, which is a credible position. This situation is now potentially causing delay of future availability of both clinical supplies and final registered, commercial versions of DepoProvera SC in Uniject.

## Next steps and milestones expected in the next six months

BD and Pfizer will hopefully conclude commercial negotiations.

- PATH will provide formal concurrence with the exclusivity terms of the BD-Pfizer agreement.
- After the BD-Pfizer agreement is signed, we will hold a collaborators' meeting including USAID, PATH, Pfizer, and BD to discuss collaborative activities in the next phase of work and plan a possible public announcement.
- If Pfizer and BD do not achieve agreement by end of 2006, PATH HealthTech and the USAID Office of Population staff should consider asking additional influential parties with appropriate high-level relationships to alert senior management (above the level currently involved in the negotiations) at both BD and Pfizer of the negtive impact to both companies if this project suffers further delay.

[‡] Uniject is a trademark of BD.

# Vasectomy technologies

## Goals of project

Under this project, HealthTech aims to:

- Verify that a cautery device (designated by the manufacturer as single use) is safe and effective for multiple uses.
- Provide technical assistance to other project partners for review of new devices, sourcing of generic devices, and sperm analysis.
- Conduct a cost-effectiveness evaluation for different vasectomy methods currently used.

## Status of project as of September 2006

After completion of the cost-effectiveness evaluation and distribution of the written results to stakeholders, the project has reduced its level of activity until discussions with USAID occur to determine next steps.

## Achievements and progress in the past six months

A manuscript on the cost-effectiveness evaluation, comparing the use of different vasectomy methods in different countries, was submitted to the journal *BMC Cost-Effectiveness and Resource Allocation*. It was determined that methods such as fascial interposition and thermal cautery, while requiring an additional investment in both training and materials, can provide increased cost-effectiveness as well as reduce the social impact of high rates of vasectomy failure. HealthTech concluded that, when possible, fascial interposition and thermal cautery should be introduced into existing vasectomy programs and trainings in order to maximize the cost-effectiveness of ongoing programs. New trainings should incorporate these methods in order to establish the most cost-effective country vasectomy program.

## Problems encountered and actions taken to resolve them

No significant problems were encountered.

## Next steps and milestones expected in the next six months

- Based on the outcome of the November 2006 meeting "Moving Vasectomy Forward," we will determine remaining needs for evaluations of vasectomy equipment and conduct assessments.
- Develop strategy to address availability and affordability of lower-cost/high-quality vasectomy equipment internationally.

# Strategic Objective 2

# Oxytocin in the Uniject device

## Goal of project

Under this project, HealthTech aims to improve and ease adoption of active management of the third stage of labor (AMTSL) and therefore reduce postpartum hemorrhage (PPH) by engaging one or more pharmaceutical producers to develop and supply oxytocin in the Uniject™[§] device (hereafter called "oxytocin-Uniject").

## Status of project as of September 2006

Results from the formal stability study of oxytocin packaged in Uniject at BIOL, our private-sector collaborator in Argentina, continue to be promising. Drug potency remains within the allowable range, and pH levels are steady. Planning with BIOL is advancing for production of clinical trial lots as are discussions with POPPHI for use of the product in Mali. Gland Pharma's (India) initial small-scale oxytocin-Uniject compatibility study showed promising results, and we are now working closely with BD India to access equipment so they can produce formal stability study lots.

## Achievements and progress in the past six months

- Three-month data from the formal stability study became available in early August 2006. These time points include data from oxytocin-Uniject stored under accelerated conditions and look positive.
- BIOL has begun to assemble components of the application dossier for Argentine FDA registration of oxytocin-Uniject.
- WHO has invited BIOL to provide technical input as WHO develops a monograph for oxytocin.
- HealthTech staff presented results of the successful Vietnam field trial of oxytocin-Uniject at the International Congress on Postpartum Hemorrhage in Goa, India.
- HealthTech staff made a site visit to Gland Pharma in India and confirmed Gland as a highly credible pharmaceutical producer, well qualified to develop and produce oxytocin-Uniject.

## Problems encountered and actions taken to resolve them

- BIOL analysis has recently indicated some impurities present in oxytocin-Uniject that are not present in the same oxytocin packaged in ampoules. BIOL, BD, and PATH are now determining the most efficient pathway to conduct the additional analytical work to precisely characterize the impurities. We expect this work will confirm that the impurities are similar to those already identified by BD as possible extractables from the plastic of the Uniject device that pose no toxicological risk, thus closing the investigation and satisfying any possible future inquiries by regulatory agencies.

## Next steps and milestones expected in the next six months

- BIOL will produce a clinical trial lot of oxytocin-Uniject to meet the needs of field studies requiring product in the 2007 and possibly 2008 timeframe. Mali is targeted as a potential 2007 field study opportunity.
- BIOL will complete regulatory documentation necessary for their application to the Argentine FDA for registration of oxytocin-Uniject, a key step on the path to commercial availability.
- PATH will assist BIOL in preparing a brief on a manufacturing supply and cost of production scenario for oxytocin-Uniject, while continuing to liaise with potential field partners.
- Gland Pharma will produce pilot lots and initiate its formal stability studies for oxytocin-Uniject.

[§] Uniject is a trademark of BD.

# Strategic Objective 3

# Reducing freezing of vaccines in the cold chain

## Goals of project

The goals of this project are to:

- Increase awareness of the extent and consequences of inadvertent vaccine freezing.
- Build global policy supporting freeze prevention.
- Facilitate development of new freeze-proof cold chain equipment.
- Assist in strengthening cold chain capacity in preparation for the introduction of new vaccines.

## Status of project as of September 2006

Freeze-prevention policy and technologies continue to be refined. WHO is moving toward adoption of freeze-prevention guidelines and Performance, Quality, and Safety (PQS) specifications that require freeze-proof refrigerators. Indonesia appears to have largely overcome its vaccine freezing problem. China and Vietnam are moving toward policy acceptance of strategies for hepatitis B vaccine birth dosing out of the cold chain to improve timeliness and coverage.

## Achievements and progress in the past six months

- HealthTech and UNICEF cosponsored a cold chain workshop in Panama. Expanded Programme on Immunization (EPI) and cold chain managers from 14 Latin American countries learned new approaches to cold chain strengthening and improving immunization access. The workshop was very well received.
- WHO has adopted a HealthTech-developed aide-memoire on the prevention of vaccine freezing and is moving toward finalizing and releasing the document. The aide-memoir is designed to raise awareness of inadvertent vaccine freezing and help countries develop strategies to solve the problem.
- In Indonesia, HealthTech evaluated the Twinbird vaccine cooler, an energy efficient refrigerator with freeze-prevention features. Performance and acceptability are good.
- Indonesia completed a review of its freeze-prevention efforts and found a dramatic reduction in cold chain freezing.
- China continued to discuss the results of PATH's out-of-cold chain study. Country and international partners met to define the pathway to national approval and routine use of the hepatitis B vaccine birth dose with vaccine vial monitors (VVMs) out of the cold chain.
- HealthTech assisted the Vietnam Ministry of Health in developing national guidelines for the use of hepatitis B vaccine out of the cold chain. A PATH study in one province showed a doubling of birth-dose coverage using the out-of-cold-chain strategy.
- Results of the cold chain study in Bolivia were accepted for publication in the journal *Vaccine*.

## Problems encountered and actions taken to resolve them

Delay in WHO's finalization of PQS specifications for refrigerators is holding up finalization and market introduction of improved refrigeration technologies, including the Twinbird and SolarChill refrigerators supported by HealthTech. HealthTech has hired a consultant for WHO to finalize refrigerator specifications, and we continue to search for ways to provide additional resources to WHO to complete the process.

### Next steps and milestones expected in the next six months

- Staff will work with WHO to finalize and release policy guidelines to reduce freezing in the cold chain and to finalize and release policy guidelines regarding use of hepatitis B vaccine out of the cold chain.
- HealthTech will support the finalization of the PQS specification for refrigerators.
- HealthTech will assist the manufacturer in submitting the Twinbird refrigerator for WHO approval and will identify opportunities for larger-scale introduction of the Twinbird refrigerator into WHO, UNICEF, and Japan International Cooperation Agency programs.
- HealthTech will identify funding and model program opportunities for introduction of the SolarChill refrigerator into public health program.
- We plan to conduct a cost-benefit analysis of new refrigerators, looking at advantages offered through improved temperature control, reduced maintenance, and reduced fuel costs. The outcome will be used to support the case for programs to invest in new refrigeration equipment.
- Results of the PATH study in China showing the effectiveness of taking hepatitis B vaccine out of the cold chain, conducted under other funding, will be published. PATH will assist with the Chinese policy shift to approve use of hepatitis B vaccine out of the cold chain with the Uniject™[**] device and VVMs.
- HealthTech will continue to identify and evaluate other promising freeze-indicator and cold box technologies. We will work with manufacturers to refine promising technologies and assist in WHO approval and commercialization.
- To help prepare cold chains to absorb the introduction of new vaccines, HealthTech will refine a cold chain equipment inventory system. A pilot system, used in Peru, will be revised, updated, and translated for use in other countries. The new system will then be installed and used in a country inventory assessment.

[**] Uniject is a trademark of BD.

# Sharps disposal technologies

## Goal of project

The project goal is to advance, test, and introduce safe needle removal and sharps disposal systems for health centers and outreach services, in order to reduce the potential transmission of disease through the use of contaminated needles.

## Status of project as of September 2006

The global call for effective waste management strategies continues to build. WHO is using Global Alliance for Vaccines and Immunization (GAVI) funding to assist countries in developing national health care waste management strategies. PATH's role in the PEPFAR-funded Making Medical Injections Safer (MMIS) project has helped many countries pilot solutions and build national interest. HealthTech has provided additional needle remover studies and tested new non-incinerator approaches to syringe disposal.

## Achievements and progress in the past six months

- In Senegal, HealthTech introduced and evaluated a low-cost approach to needle removal that uses locally available containers. The partially reusable device could make needle removal affordable in low-resource settings. User input showed strong support for this approach.
- In Indonesia, HealthTech began evaluation of three prototype syringe melters. The systems are low cost and provide a simple non-incineration approach to syringe volume reduction and disinfection, thus simplifying final disposal.
- In India, HealthTech conducted a study of how needle removal is used to facilitate injection safety and create a syringe plastic recycling program. An economic analysis of the needle removal-recycling program is underway.
- In Vietnam, HealthTech contributed technical oversight to a study of needle removers in commune health centers. Needle removers were credited with making a dramatic improvement in the cleanliness of health centers and disappearance of syringe waste from public areas. Needle removers are now included in national policy as an option for use in health centers.
- In Kenya, HealthTech helped the MMIS project develop a new low-cost needle pit design. The new approach, using a buried plastic barrel, will speed installation and reduce costs and is being introduced in Kenya health care facilities.
- PATH's training manual on sharps waste management continues to be disseminated and translated in several countries. The manual has been posted on WHO's safe injection website.
- HealthTech cosupported PATH participation in a WHO meeting in Nairobi where WHO unveiled a plan to support country development of national medical waste planning exercises.
- HealthTech contributed to the development of WHO's newest health care waste guidance document, "Management of waste from injection activities at the district level." Several HealthTech-supported technologies, including needle cutters, needle pits, needle barrels, and needle poppers are recommended as practical options in the manual.

## Problems encountered and actions taken to resolve them

- WHO headquarters continues to hold a neutral position on needle removers. To help them resolve their inaction, PATH continues to supply field data and support materials showing the safe routine use of needle removers.
- WHO has stopped work on finalization of the PQS process. Without specifications for needle removers, manufacturers and purchasers are not able to move forward. PATH has helped WHO

refine draft needle remover specifications and continues to search for ways to restart the PQS process.

.

### Next steps and milestones expected in the next six months

- HealthTech will continue to provide assistance in the development of policies and guidelines and the adoption of effective sharps management technologies and practices.
- With WHO, we will continue to advance global consensus on best practices of medical waste management. HealthTech will provide technical guidance in the development of guidelines for the selecton of equipment and national planning processes.
- We will engage international agencies such as the GAVI and the World Bank to develop strategies and funding mechanisms for sustainable implementation of medical waste systems.
- HealthTech will continue to assist WHO in implementing GAVI-funded activities to develop national health care waste plans for GAVI countries.
- We will develop technical guidance materials for needle removers and disseminate them via PEPFAR countries and TechNet.
- HealthTech staff will use the Safe Injection Global Network (SIGN) and TechNet meetings to disseminate updated information and encourage feedback on improved practices in sharps management strategies and technologies.
- Following up on a successful evaluation of a low-cost needle popper and cutter in Senegal, we will refine the design of the concept and approach manufacturers to discuss commercialization.
- Over the next six months, we will identify successful introductions of non-burning disposal systems, such as autoclaving or shredding. We will document introduction issues, clarify equipment selections, and disseminate lessons.
- To make reconstitution of lyophilized vaccines safer and needle-free, we will work with WHO’s aerosolized measles vaccine group to refine and test a plastic-needle reconstitution syringe.

# Gentamicin in the Uniject device

## Goal of project

The goal of this project is to create a sustainable supply of gentamicin in the Uniject™[††] device (hereafter called "gentamicin-Uniject") so this innovative combination can be fully evaluated for use in the treatment of neonatal infections.

## Status of project as of September 2006

Results from the formal stability study of gentamicin packaged in Uniject at BIOL, our private-sector collaborator in Argentina, continue to be promising. Drug potency remains within the allowable range and pH levels are steady. Planning with BIOL is advancing for production of lots of gentamicin-Uniject for clinical trials. A study in Nepal during 2007 will evaluate use of gentamicin-Uniject in the field.

## Achievements and progress in the past six months

- Three-month data from the formal stability study became available in early August. As noted above, results were all within allowable ranges.
- PATH and the Nepal Family Health Project have received USAID funding to collaborate in the design and implementation of a design-stage field evaluation of gentamicin-Uniject, with completion targeted for autumn 2007.
- BIOL has begun to assemble components of the application dossier for Argentine FDA registration of gentamicin-Uniject, which is a critical path step in the production of the product.

## Problems encountered and actions taken to resolve them

- Saving Newborn Lives, which originally was going to sponsor a trial of gentamicin-Uniect as part of a larger study of gentamicin for neonates, did not extend or renew their study in Bangladesh. This study had represented an opportunity for early field evaluation of gentamicin-Uniject. Fortunately, a funded opportunity has emerged (see above) for field evaluation in Nepal with a different organization.

## Next steps and milestones expected in the next six months

- BIOL will produce a clinical trial lot of gentamicin-Uniject to meet the needs of field studies requiring product in the 2007–2008 timeframe. Planning for this is advancing well.
- BIOL will complete regulatory documentation necessary for their application to the Argentine FDA for registration of gentamicin-Uniject, a key step on the path to eventual commercial availability.
- HealthTech will assist BIOL in preparing a brief on a manufacturing supply and cost of production scenario for gentamicin-Uniject, while continuing to liaise with potential field partners.

[††] Uniject is a trademark of BD.

# Neonatal resuscitation

## Goal of project

The goal of this project is to increase understanding and awareness of the availability and performance of neonatal resuscitators among the international community and to enhance availability of appropriate devices in low-resource settings, particularly in Africa and Asia.

## Status of project as of September 2006

During the past six months, results from work related to neonatal resuscitation have been disseminated in various venues. Funds to implement a collaborative activity to assess essential newborn care in India have been secured and the evaluation has been launched. The necessary procurement and data collection for a revised version of the "Practical Selection of Neonatal Resuscitators–A Field Guide" has been completed.

## Achievements and progress in the past six months

- A manuscript on the context-of-use survey was submitted to the *Journal of Tropical Pediatrics*; the journal has requested that the manuscript be edited for inclusion as a research brief.
- An abstract on the context-of-use survey was accepted for a poster presentation at the American Public Health Association annual conference in Boston, November 2006.
- Posters of the context-of-use survey and bench and user evaluations of devices were created and displayed at the NewbornNet Indiamother meeting in Delhi, India, in July 2006.
- Provision of technical assistance through a subcontract with F2H, the Indonesian organization that currently manufactures tube and mask devices. With technical and financial assistance from HealthTech, F2H is developing a bag and mask resuscitator for the Indonesian market.
- A global inventory of available neonatal resuscitation devices has been completed; a compendium of details of over 100 identified devices was produced in June 2006 and has been posted to the PATH website for public reference.
- Data collection and limited user evaluation for the expansion and revision of a "Practical Selection of Neonatal Resuscitators–A Field Guide" has been completed. The revised version will focus on reusable, silicone bag and mask devices that cost less than US$30 each.
- A collaborative effort with the Government of India, USAID/India, WHO-India office, UNICEF, IndiaCLEN, and PATH's office in India to conduct a situational analysis of essential newborn care (primarily neonatal resuscitation) in selected states in India was jointly planned and launched. HealthTech negotiated a sub-agreement with a research partner, IndiaCLEN Program Evaluation Network, to jointly conduct this work. Protocols were finalized in August 2006. A non-research determination was approved for this work by PATH's committee in September 2006.

## Problems encountered and actions taken to resolve them

- Limited funds for work other than the India essential newborn evaluation require a redirection of project strategy. In the next quarter, the HealthTech Product Evaluation Plan will be revised to indicate a redirection of remaining funds to collect and disseminate information relevant to advocacy with stakeholders at UNICEF to include lower-cost, high-quality devices in their catalog.

## Next steps and milestones expected in the next six months

- A market assessment of existing and/or redesigned devices in the African region will be conducted. This assessment will provide baseline information regarding availability, affordability, and use of current products. Results from the market research will help us understand potential

demand and identify strategic opportunities to further the project goal of increasing availability of high-quality and low-cost neonatal resuscitators by building supply and distribution channels. The first phase of this activity will take place in South Africa which was selected for several reasons including:

- There is local manufacture and distribution of a neonatal resuscitator.
- There is interest by local stakeholders in improving access to high-quality and affordable devices.
- South Africa has sufficient resources to purchase neonatal resuscitators.
- Finalization and dissemination of revised "Practical Selection of Neonatal Resuscitators–A Field Guide" to key stakeholders.
- Dissemination efforts and project strategy will be realigned to produce information for use in advocacy efforts directed towards encouraging UNICEF to include low-cost, high-quality devices in their catalog.
- A manuscript on bench and user evaluations of 11 devices was rejected by a peer-reviewed journal (*Archives of Childhood Disease*). The manuscript will be edited based on editorial comments received and emphasize an increased focus on lower-cost, reusable resuscitators. The edited manuscript will be resubmitted elsewhere.
- A manuscript on the context-of-use survey will be edited and resubmitted to the *Journal of Tropical Pediatrics* as a research brief.
- If data collection (through the market assessment in South Africa and possibly other sites) identifies substantial demand for resuscitation devices, discussions with manufacturers of the most appropriate devices identified through the global inventory process will be initiated in order to determine a suitable commercialization strategy for the African region.
- An informal site survey will be conducted among PATH travelers to gain information about neonatal resuscitator device supply and use at the local level.
- Backstopping and technical assistance will be provided as needed to the study entitled India Essential Newborn Care Situation and Needs in National Rural Health Mission Priority States in India.

# Retinol Binding Protein Enzyme Immunoassay (RBP-EIA)

## Goal of project

The goal is to enhance the reliability and ease of assessment of vitamin A deficiency (VAD) and decrease the associated cost. Specific objectives are to improve the consistency of results of vitamin A assessment, including ease of specimen analysis and interpretation, and to improve the reliability of VAD estimates.

## Status of project as of September 2006

We continue to support the introduction and use of the RBP-EIA into the public health arena. We are currently working with Scimedx Corporation, the private-sector licensee of the product, to refine some of the test kit components in response to feedback from end users.

## Achievements and progress in the past six months

- We met with staff from the USAID Nutrition Division and the USAID-supported program, A2Z, in May 2006 to provide an update on the status of the RBP-EIA.
- We worked with Scimedx Corporation to address and resolve issues raised by end users to make the test kit easier to use by increasing the conjugate volume and putting the calibrator into three separate tubes.
- Validation results from Cambodia were published in a refereed journal: Hix J, Rasca P, Morgan J, Denna S, Panagides D, Tam M, and Shankar A. "Validation of a rapid enzyme immunoassay for the quantitation of retinol binding protein to assess vitamin A status within populations." *European Journal of Clinical Nutrition* advance online publication, May 31, 2006.
- HealthTech supported the evaluation of elution procedures for measuring retinol-binding protein in dried blood spots by the University of Washington. The report was completed and findings presented to PATH in August 2006. There was no significant difference between RBP in serum verses plasma. Recovery of RBP from dried blood spot (DBS) specimens was, on average, 90 percent of RBP in serum and 94 percent of RBP in plasma, and varied slightly by elution protocol used, but did not vary by blood collection method. Elution procedures using higher volumes of diluent produced results more similar to serum values.
- Three abstracts were submitted to the Micronutrient Forum (August 2006) based on RBP-EIA team-supported activities or analyses:
    - Collection, processing, storage, and transport of dry blood spot samples for the Assessment of VAD in the Uganda Demographic and Health Survey.
    - Validation of collection and elution procedures for measurements of retinol binding protein in dried blood spot specimens.
    - Feasibility of Using Capillary Blood Specimens for the Assessment of VAD in Low-Resource Settings.

## Problems encountered and actions taken to resolve them

- During our meetings with key stakeholders in Washington, DC, we specifically requested collaboration with the USAID project A2Z as they move forward to implement micronutrient programs but were informed that they have limited budgets for monitoring and evaluation. We also asked that the Micronutrient Forum steering committee endorse the RBP-EIA; however, they expressed that they would need to see validation of the RBP-EIA using DBS before issuing an endorsement for the RBP-EIA test. We do not have the budget to support this type of analysis.

### Next steps and milestones expected in the next six months

- Identify and provide support to new users of the RBP-EIA to assess VAD.
- Participate in the Micronutrient Forum in April 2007 to present results and network with potential users of the RBP-EIA.
- Finalize refinements to the RBP-EIA test kit and support evaluation of changes to the test kit.

# Strategic Objective 4

# Immunochromatographic strip test for chlamydia

## Goals of project

The goals of this project are to:

- Establish commercial availability of a rapid chlamydia test (CT) for use in developing countries.
- Publish data supporting the utility of this test in the developing world.
- Achieve endorsement of the test by WHO.

## Status of project as of September 2006

- We recently completed a large evaluation (N=1,840) of the CT immunochromatographic strip (ICS) test among high-risk women in four cities in Bolivia. This evaluation involved comparing syndromic management, the CT ICS test, ELISA, and polymerase chain reaction for determining CT status. Data analysis is underway, but initial results show that the performance of our test was poor (less than 50 percent sensitive).
- Our work with the Global Network for Perinatal and Reproductive Health to design a study of CT diagnosis algorithms (including rapid tests) in Colombia continues. The Ministry of Health has given preliminary support for the study and agreed to provide funding for part of the work. We are currently seeking additional funding to support implementation of this work.
- We completed our work on a fluorescence-based signal enhancement system for the CT ICS test. We were able to improve the lowest level of detection by ten-fold through this work.

## Achievements and progress in the past six months

- We completed enrollment for our study in Bolivia and are analyzing results. This study also included the evaluation of new specimen collection devices using a randomized design. Preliminary experiments at PATH showed that flocked nylon swabs may collect and release significantly more analyte than standard Dacron swabs.

## Problems encountered and actions taken to resolve them

- Testing results from ELISA assays from collaborating laboratories in Bolivia were variable in terms of performance. Specifically, a single laboratory in El Alto (a slum next to La Paz), which serves the largest group of high-risk women in the country (CT prevalence approximately 17 percent) had poor technique and quality control for their ELISA testing. In collaboration with our local partners we retrained laboratory staff in this laboratory and improved the assay performance.

## Next steps and milestones expected in the next six months

- We plan to write and submit at least two manuscripts to peer-reviewed journals which summarize various aspects of the Bolivia study.
- If the final results of the Bolivia study indicate that more improvements in the test are required and could make a difference, we will re-optimize the test and conduct a second field evaluation. These activities are subject to availability of funding.

# CD4+ cell count diagnostic project

## Goal of project

Our goal is to develop a simple, semiquantitative test for monitoring CD4+ cell counts in HIV-positive populations. This technology will:

- Allow health care workers to quickly and accurately monitor the immunological status of their HIV-positive patients.
- Provide data for clinicians making important decisions about initiating, stopping (through structured treatment interruption), or changing antiretroviral therapy drug regimens.
- Eliminate the most important barrier to appropriate distribution of drug therapies that reduce morbidity; reduce viral load, and therefore reduce transmission; and most importantly, empower clinicians and patients to control the expanding epidemic.

## Status of project as of September 2006

We are currently optimizing the development of a simple fluorescence-based CD4+ cell detection system in collaboration with our private-sector partner, PortaScience, and co-funding from the Doris Duke Foundation. We are also simplifying a magnetic bead-based purification system, which will be rapid and less expensive than current bead-based methods and not require extensive capital equipment and temperature control.

## Achievements and progress in the past six months

- We have developed a prototype system for purification of CD4+ cells from whole blood which uses commercially available magnetic beads and reagents. We have simplified this system and hope to improve its performance in the coming months. It will be used in conjunction with the detection system.
- We have determined a lower limit of detection with the CD4+ cell system which is commensurate with our lowest semiquantitative category (less than 200 cells).

## Problems encountered and actions taken to resolve them

- Our prototype purification system did not give us the desired yield and purity needed for our detection system. To resolve this issue we initiated a collaboration with researchers at the University of Washington, Department of Bioengineering, who have developed several unique “smart” polymer-based systems for capture of cells and proteins from complex mixtures. Experiments are ongoing.

## Next steps and milestones expected in the next six months

- We will evaluate our purification and detection systems with clinically collected blood specimens from HIV-positive individuals who present to Harborview Medical Center (Seattle, WA) with low (less than 200), borderline (between 200 to 350), and sufficient (greater than 350) CD4+ cell counts. We also have recently submitted a proposal to the Imperial College under their CD4 Initiative for funding to scale up this project to a level that would allow us to reach major product development milestones beyond prototyping. We should hear about the funding within the next month or so.

# Microbicide applicator project

## Goal of project

The goal of this project is to ensure that safe, appropriate, affordable applicators for microbicides are available for use in low-resource settings at the time of microbicide introduction.

## Status of project as of September 2006

We are focusing on determining the equivalency of the user-filled applicator in relation to the HTI prefilled applicator currently being used in clinical trials. In addition we are researching the regulatory pathways for applicators in southern Africa, obtaining up-to-date applicator cost information on applicators, and developing a novel applicator prototype that will ensure proper dose filling and dose delivery.

## Achievements and progress in the past six months

- HealthTech made three presentations at the Microbicides 2006 conference in Cape Town, South Africa (April 2006). At a WHO-sponsored pre-conference meeting of regulatory representatives from six southern African countries, we spoke about broadening women's options for microbicide delivery through use of alternative applicators. This led to a discussion about what information would be needed to incorporate alternative delivery systems into an application for regulatory approval. The second presentation, given to the International Working Group on Microbicides, discussed trade-offs between microbicide applicator characteristics that affect user acceptability and identified the need to incorporate alternative delivery systems into regulatory applications. More than 150 people attended the third PATH presentation held during the Increasing Access section of the conference on recent work to identify and evaluate characteristics of microbicide applicators that affect acceptability and accessibility, including proposed next steps. PATH made contact with two microbicide sponsors at the meeting and discussed the possibility of initiating a study in 2007 with their gels.
- To determine research requirements from southern African regulatory bodies, HealthTech is adapting the presentation made at the Microbicides 2006 conference to outline the clinical evaluation steps recommended by the USFDA for approval of alternative delivery and pose a series of questions/next steps for the South African regulatory group to consider. HealthTech will contact WHO and Reproductive Health Research Unit representatives to facilitate collecting this information and sharing this plan with the regulatory groups.
- The study to assess user compliance, acceptability, and dose delivery of TekPak user-filled paper applicators with a placebo gel began the week of September 19. There was a delay due to an unexpected change in the KY jelly packaging (see further details below). To date, six subjects have been enrolled; enrollment is expected to increase substantially during October and November.
- HealthTech is carrying out a dose delivery study in house to compare HTI prefilled and Tekpak user-filled applicators using hydroxyethyl cellulose (HEC) placebo. We have repackaged HEC placebo taken from surplus prefilled applicators so it can be used for user-filled applicators. This requires technical testing and experimentation with packaging gel into aluminum multi-dose tubes to avoid air bubbles and other technical variations.
- For the study to determine cost "break points" for manufacturing and supply of microbicide delivery methods, we are currently reviewing the results from previous domestic and international applicator costing evaluations and developing a framework for updating these figures. Concurrently, we are reestablishing industrial and consultant contacts and expanding the content of our survey regarding international manufacturers and fillers.

- In the effort to design a first-generation, dose-metered applicator prototype that could be used for microbicides and/or cervical barriers, we have developed a list of performance specifications that have been informed by our previous research on vaginal microbicide applicators. Product development experts have presented two lead design concepts.
- In June 2006, HealthTech contacted several microbicide sponsors to assess their interest in evaluating delivery of their microbicide gel with either the user-filled applicator or other delivery devices. We received samples from Contraceptive Research and Development Program (CONRAD) and the Population Council. Under separate funding, we have developed tests to assess the physical characteristics of these microbicide gels that could affect acceptability such as viscosity (compared to KY gel) and surface affinity to various materials. PATH evaluated the capacity of the SILCS Diaphragm to deliver the recommended dosage as a preliminary feasibility check.

### Problems encountered and actions taken to resolve them

- The clinical study in the Dominican Republic was delayed in starting due to an issue with the KY jelly packaging. The study was designed to use KY jelly as the inert substance used to fill the Tekpak applicators. The manufacturer no longer packages KY in multi-dose foil tubes and uses plastic tubes instead. This impacted the ability of study participants to fill the applicators per the user instructions. Because multi-dose foil tubes are to be used for the microbicide, we investigated whether there was another KY-like jelly that is packaged in a foil tube. After in-house testing, we found that Surgilube closely approximates KY jelly and is packaged in a multi-dose foil/plastic tube that closely approximates a foil tube. This study modification to use Surgilube was approved by the PATH Human Subjects Protection Committee and the local Dominican Republic institutional review board. Due to the delayed study start date, data will not be available until March/April 2007.

### Next steps and milestones expected in the next six months

- PATH will advance the two leading design concepts toward proof-of-concept prototypes of microbicides applicators. We will conduct bench testing to evaluate physical performance criteria and mock-user testing to collect information from naïve users about acceptability.
- Study results from the Dominican Republic study will be available, and plans can be made for the Phase 1 safety study.

# Packaging solutions to improve provision of nevirapine in PMTCT programs

## Goal of project

The goal is to reduce mother-to-child transmission of HIV by improving antiretroviral therapy coverage in prevention of mother-to-child transmission (PMTCT) programs. HealthTech focuses on developing, evaluating, and facilitating introduction of improved single-dose packaging solutions for nevirapine (NVP) oral suspension.

## Status of project as of September 2006

Technical development work on this project was completed in January 2006. The proposed packaging improvement is a self-sealing foil pouch designed to surround and protect an oral dosing syringe that can be securely capped once the nurse fills it with NVP oral suspension (hereafter referred to as syrup). The NVP infant-dose pouch is also labeled with pictorial instructions as well as expiry information. A pilot introduction of this improved packaging was successfully completed in Kenya in July 2006, with plans to expand use of the NVP infant-dose pouch nationally in Kenya.

## Achievements and progress in the past six months

- The Kenya pilot introduction of the NVP infant-dose pouch was completed and preliminary results have been written up and disseminated. Approximately 543 pouched doses of NVP syrup in Exacta-Med®[##] dispensers were provided to HIV-positive pregnant women by health workers in facilities in advance of giving birth. The pilot results showed high acceptability of the approach among the women and the providers. A summary of the results has been sent to USAID under separate cover.
- We prepared and published a sourcing manual for the NVP pouch to facilitate procurement of pouches on the PATH website. The site also includes links to a training manual to assist programs in training staff on introduction of the pouch. These resources can be found at: http://www.path.org/projects/nevirapine_pouch_resources.php
- In August 2006, HealthTech team members attended the International AIDS Conference in Toronto (using funding from the Sapling Foundation—a project co-funder) and disseminated project results through meetings with partners as well as displaying the project at the PATH booth.
- In September 2006, a stakeholders meeting was held in Kenya with more than 70 participants representing every province within the country and many of the partners. HealthTech presented findings from the pilot introduction and discussed next steps for broader introduction of the take-home approach. The Ministry of Health (National HIV/AIDS and STD Control Programme and Division of Reproductive Health) recommended the NVP infant-dose pouch be rolled out nationally for use in all PMTCT sites.

## Problems encountered and actions taken to resolve them

- Boehringer Ingelheim (BI), the manufacturer of Viramune®[§§] -brand NVP has yet to determine if the NVP infant-dose pouch will be incorporated into their PMTCT Donation Programme (currently providing NVP syrup, tablets, and Exacta-Med dispensers). PATH met with BI to clarify the issues and next steps needed for BI to reach a decision. PATH agreed to prepare a summary report on the development work to date and expects a formal decision will be made before the end of 2006.

[##] Exacta-Med is a registered trademark of Baxa Corporation.
[§§] Viramune is a registered trademark of Boehringer Ingelheim.

### Next steps and milestones expected in the next six months

- A supply of 68,000 pouches has arrived in Kenya for national PMTCT program use. HealthTech will work with the MOH and other partners to finalize a plan for distribution as well as a strategy for sustainable supply.
- A final report on the development phase of the NVP infant-dose pouch, requested by BI, will be completed.
- Documentation of the technical work to develop improved packaging will be completed.
- A formal decision from BI as to whether the NVP infant-dose pouch will be incorporated into the PMTCT Donation Programme should be made.
- Assistance to organizations such as Elizabeth Glaser Pediatric AIDS Foundation and Family Health International who are considering broader introduction of the NVP infant-dose pouch will be provided. Approximately 50,000 pouches are available to seed programs interested in using the pouch.

# Strategic Objective 5

# Rapid diagnostics for tuberculosis

## Goals of project

The goals of this project are to:

- Develop or evaluate an accurate and simple test for tuberculosis (TB) that is affordable to populations in the developing world.
- Understand the need and market for rapid diagnostics for TB in order to make informed decisions about investments in development of tests.

## Status of project as of September 2006

We are currently collaborating with Sequella Inc., a commercial company that has developed a promising transdermal patch test for detection of active TB disease. Early evaluations of the test in the Philippines and South Africa by Sequella show high sensitivity (greater than 85 percent) and specificity (greater than 92 percent) when compared to gold standard culture results. We are initiating dose-finding and performance evaluation studies in Ukraine in the coming months, working with the PATH staff and several local TB clinics in Kiev and Donetsk.

## Achievements and progress in the past six months

- We signed a collaboration agreement with Sequella Inc. We will be conducting the study while they supply the tests and provide technical assistance in the field. In return, Sequella has agreed to publish the results from the study regardless of outcome. This will allow us to provide the TB community with an objective review of the test performance in an important clinical setting.
- We developed protocols for both the dose-finding and performance evaluation studies. We will submit these protocols to PATH and the local institutional review board in the coming weeks.

## Problems encountered and actions take to resolve them

- The original study included a market study prior to clinical evaluations of the patch test. After discussions with our Ukraine country office staff, we realized that a market study for TB diagnostics would not be feasible given our study timeline and budget. We decided to move forward with the clinical evaluations and will revisit the idea of a market study at a later date.

## Next steps and milestones expected in the next six months

- We expect to complete a study of 75 individuals that will determine the optimal dose for the patch test.
- We will also prepare for the follow-on performance evaluation study on 315 patients, which is expected to begin by the second quarter of 2007.

mfrp24603