

HealthTech IV
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Executive summary

The following are significant results and achievements over the past six months of the HealthTech project:

- Reinitiated discussions among United States Agency for International Development (USAID), Pfizer, and Program for Appropriate Technology in Health (PATH) regarding opportunities and challenges in creating availability of the new formulation of depot medroxyprogesterone acetate (DMPA) in the Uniject™* device. The Pfizer team plans to pursue final technical feasibility issues during late 2003 and early 2004. They have high confidence of technical success, but need to confirm that minor adjustments to the formulation of their new DMPA will enhance its stability in the Uniject device.
- Studies were completed in India and Bangladesh to verify a safe and effective dosage for once-daily gentamicin-Uniject in neonates. The Data and Safety Monitoring Board (DSMB) concluded that the objectives for the pharmacokinetic testing of gentamicin have been met. The following dosages are now recommended for use in the Uniject device: 13.5 mg q 24 h for patients ≥ 2500 g, 10 mg q 24 h for patients 2000 to 2499 g, and 10 mg q 48 h for patients < 2000 g. However, final recommendations for use of these dosages is pending until the results of hearing tests on the study patients are available.
- The Cold Chain Technologies team developed a set of eight educational and training posters to reinforce proper refrigeration, transport, and monitoring procedures. These materials have been translated into French and distributed to African regional cold chain managers. They were also used for training and distributed at a SEARO immunization conference. One was translated into Indonesian and local funding was obtained to print and distribute 8,000 posters to every health center in the country.
- The latest design of the mass campaign jet injector was presented to the Measles Steering Committee Meeting April 29 to 30 at the World Health Organization (WHO) in Geneva. Positive response was generated, and the technology was recognized as being on a faster track towards field introduction and market use, once safety testing could be conducted.
- A cost model, implemented by Instituto Nacional de Salud Pública, demonstrates the cost-effectiveness and impact of the jet injector in mass immunization campaigns, compared to the use of auto-disable syringes.
- PATH organized a workshop in July in Indonesia to present the national policy on sharps waste management in primary health facilities to provincial immunization managers and to demonstrate technical solutions for sharps disposal. The workshop was significant in that it raised awareness of issues of operation, community acceptance, syringe collection and transportation systems, responsibility and budget.
- PATH continued the needle remover demonstration project in India, which will end in November 2003. Nine sites in Delhi and Jaipur, including two control sites, are participating. This project will document the performance, acceptability, and effect of needle removers on immunization waste management practices. Data are being gathered on device durability, reliability, ease of use, waste volumes, needle disposal practices, syringe disposal practices, and needle-stick injury. By September, data were collected on more than 5,000 person-days of use, with more than 34,000 needles removed in both static and outreach settings.

* Uniject is a trademark of BD.

- An article describing the validation of the RBP-EIA titled, “Development of a rapid enzyme immunoassay for the detection of retinol binding protein” has been accepted for publication in the *American Journal of Clinical Nutrition*.
- The RBP-EIA device has been licensed to Scimedx, Inc., PATH’s commercial collaborator for this technology, and the official technology transfer was conducted in June 2003. Development of the prototype for scale-up began thereafter. Scimedx has successfully produced a RBP-EIA prototype based on original standard operating procedures (SOPs), in preparation for manufacturing the test.
- Data from the adult tuberculosis (TB) study of the PATH TB immunochromatographic strip (ICS) test in Botswana was presented as a poster at the American Thoracic Society meeting in May 2003 and has been accepted for publication in the *Journal of Infectious Diseases*.
- Final analysis of clinical data from a prospective field evaluation of the TB ICS test conducted in Ukraine has been completed. The sensitivity and specificity of the test in this population is 74.7 percent and 64.8 percent, respectively, when compared to AFB culture. The high false positive rate of the TB ICS test is surprising, since this has not been observed in other studies, and analysis is ongoing to identify the factors that may have contributed to this high false positive rate.
- Results from a prospective field evaluation of the gonorrhea (GC) ICS test in South Africa were presented at the International Society for Sexually Transmitted Diseases Research conference in Ottawa, Canada. This field evaluation was significant because the results suggest that vaginal exudates can be effectively used as specimens, which are easier to obtain and much less invasive compared with the standard method of collecting cervical swabs for GC testing.
- GC ICS test kits have been shipped to Benin for WHO’s Sexually Transmitted Diseases Diagnostics Initiative (SDI) field evaluations. This multi-site trial, entitled “Clinic-based evaluation of rapid tests for the diagnosis of gonococcal infections,” will provide field validation data from several thousand women in a “multi-round” format.
- The cloned monoclonal malaria antibody supernatants were purified and the three monoclonal antibodies in the ICS test format were screened. Preliminary data, using a small number of clinical samples, indicates that the purified monoclonals are sensitive and specific to PfHRP-2. These preliminary results indicate that these newly developed antibodies may become a cost-effective alternative to the currently available antibodies.
- A total of 2,606 women had been enrolled and interviewed so far in the delivery kit evaluation in Tanzania. Preliminary results are favorable. Regression modeling indicates that having a bath before delivery and use of the kit had a significant impact on puerperal sepsis, and that the probability of developing cord infection is smallest for infants whose mothers had a bath before delivery and who used the kit. Cross tabulations indicated that there is a lower chance of developing a cord infection if a new tie (included in kit) is used.
- PATH has been nominated as a laureate by the Tech Museum of Innovation to receive an award for technology benefiting humanity. The Tech Museum awards were developed to recognize the need to bridge existing technology in emerging countries and emerging technologies in developed countries. PATH’s nomination was based on the Uniject device developed under the HealthTech program. Winners will be announced in October.

Vaccine Vial Monitors

Health Need Addressed

Vaccines must be protected from excessive heat exposure during storage and transport to the point of use, or they may not provide sufficient immunity to children who receive them. Appropriate temperature storage is difficult to maintain as vaccine is transported from the manufacturer to the recipient via the cold chain. In the past, health workers had no way to verify whether vaccine was potent or useless, since vaccine does not change appearance when it degrades. The implications of this problem have been enormous. Immunization programs have adopted conservative guidelines for handling vaccine and disposal of vaccine when heat exposure is suspected, often resulting in disposal of good vaccine in programs where resources are already scarce.

HealthTech IV Solution and Potential Impact

Vaccine Vial Monitors (VVMs) are small, circular indicators that are printed directly on vial labels or adhered to the tops of vials, ampoules, or tubes. The inner square of the VVM changes color irreversibly from light to dark with exposure to heat over time. By comparing the color of the inner square to the surrounding reference color, a health worker can determine the extent to which the vaccine has been exposed to heat. VVMs provide health workers with a clear warning when vaccine should be discarded due to heat exposure. At minimum, they allow health workers to prevent delivery of heat-damaged vaccine to children and reduce the discard of usable vaccine.

Polio eradication national immunization days have demonstrated that VVMs can be used when transporting vaccine to remote areas without compromising the quality of the vaccine, even with the most heat labile of all currently used vaccines. VVMs are a powerful managerial tool to enable immunization programs to identify and make changes to their cold chain infrastructures to minimize costs and decrease the chances of damaging freeze-sensitive vaccines. Once VVMs are on all vaccines, the level of vaccine wastage indicated could become the basis on which a particular cold chain is managed. Investment will be needed where wastage is high, and flexibility may be permitted where wastage is low. Thus the cold chain may be “tuned” to eliminate costly redundancies inherent in the system today.

Milestones and Accomplishments Achieved in the Past Six Months

Ensuring Access—Removing Impediments to Vaccine Vial Monitor Implementation

- GAVI pressure on procurement policy appears to be succeeding for the vaccines provided by the Vaccine Fund. Most manufacturers now target the end of 2004 for other vaccines.
- As of September 2003, all five suppliers of oral polio vaccine (OPV) to the United Nations continue to include VVMs on their products. A total of 14 out of the 25 UN prequalified suppliers of EPI vaccines have now included VVMs. Of the 65 vaccine products from these sources, 26 have VVMs attached of which 21 are non-OPV products. VVMs are therefore available on all OPV and a portion of BCG, DT, DTP, DTP-HepB., DTP-Hib, Hib, yellow fever, measles, MR, MMR, hepatitis B, and tetanus-toxoid vaccines supplied through UNICEF.
- Annual demand for VVMs for 2002 was 141,616,000 units. From April to September 2003, approximately 86,447,000 units were sold to vaccine producers, up 33 percent over the previous six-month period (64,930,000). The demand for VVMs supplied for non-OPV products rose by 99 percent not including the donations.

- LifeLines Technologies also makes donations of VVMs to the UNICEF Maternal and Neonatal Tetanus Elimination project. From April 2002 through March 2003, 3 million VVMs were donated, and from April 2003 through September 2003, 2 million VVMs were donated. This specific donation program is now completed with 9 million VVMs donated over a three-year period for this project.
- The GAVI July 2003 board meeting received a report from industry on the status of the implementation of VVMs. The Board report concluded “adoption of VVMs by manufacturers is accelerating though behind the schedule proposed by the Board. VVMs will be available on all mono-valent hepatitis B and DTP-HepB vaccines by end 2003. VVMs will be available on the DTP-HepB-Hib during 2004. Yellow fever is the only Vaccine Fund-purchased vaccine for which VVMs will not be fully available.”
- Aventis Pasteur has announced its intent and now shows progress towards implementing the use of VVMs on Vaccine Fund provided vaccines by the end of 2003.

Informed Selection—Technical Assistance to Immunization Programs.

- The Pan American Health Organization (PAHO) has in the past rejected the use of VVMs in the region. In August 2003, however, they invited WHO to make a presentation on VVMs in the management of the cold chain at a technical meeting involving most of their national immunization program managers, although this has not yet impacted the vaccine procurement policy of the PAHO Revolving Fund.
- The July 2003 GAVI Immunization Focus newsletter included a major article on the benefits of VVMs and the current problems related to their implementation on all vaccines. The article informed the GAVI board and other stakeholders.
- A study was conducted in Nepal, Turkey, and Zimbabwe by WHO in 2002 and presented in 2003 to determine the impact of transporting freeze-sensitive vaccines using chilled-water packs. VVMs were used in the study to determine the heat exposure of these vaccines. PATH has used this data and the time-temperature characteristics of the four categories of VVM to estimate the proportion of usable storage life that would be consumed, comparing a variety of freeze prevention measures that could be adopted. This powerful comparator, used in meetings of the Technologies and Operations Panel (TOP) of WHO, is helping to convince the vaccine industry that vaccines are at minimal risk of heat exposure when the cold chain is modified to protect them against freezing.
- A technical status document has been prepared by Lifelines with assistance from PATH. The document responds to questions raised in the GAVE board meeting in July 2003 regarding VVM implementation. The document is to be circulated to members of the board and disseminated to all vaccine manufacturers.
- The PATH study on the demand for vaccines over the next ten years and other sources are being used to build a market picture for VVMs that will help clarify future demand.

Problems Encountered and Actions Taken

- **Problem:** Although all major UNICEF vaccine suppliers include VVMs with OPV and have pledged to include VVMs on vaccines provided by the Vaccine Fund by the end of 2003, several major manufacturers still express no interest in VVMs for remaining vaccines.
- **Problem:** The supply of VVMs has been dominated by the supply of OPV since 1996 and is now stable at approximately 125 million in 2002 and 2003. The VVM supply for OPV is

expected to remain stable during the next year and decline starting in 2006 as polio eradication activities are scaled down. Although the supply of VVMs for other vaccines continues to rise from 1.5 million in 2000 to 22 million in 2003, with an expectation for 46 million in 2004, it is not clear whether the rise will be fast enough or great enough to offset the decline of the need for VVMs for OPV.

- **Problem:** UNICEF continues to use a distribution policy that does not take into account VVM implementation. Countries still do not know whether or not any given shipment will receive VVMs and cannot plan for their use.
- **Problem:** Serum Institute of India (SII) currently represents developing-country vaccine manufacturers on the Global Alliance for Vaccines and Immunization (GAVI) board and has used the opportunity to raise numerous technical issues regarding the implementation of VVMs. SII has corresponded on these issues to WHO, PATH, and the editor of the GAVI Immunization Focus newsletter. Although this appears to not impede their own implementation of VVMs, their public voice may well be influencing other developing-country vaccine manufacturers.
- **Problem:** Due to the delayed introduction of VVMs on all vaccines, it has not been possible to launch a project that was requested by the GAVI Task Force on Implementation to establish and evaluate a system of monitoring and reporting on vaccine wastage related to VVM status within the routine monthly reporting system.

Action: PATH will continue to monitor the situation, provide technical assistance as needed and as requested, and advocate in all public forums for the logical and consistent use of VVMs on all vaccines.

Status of Project as of September 2003

Since March 1996, all OPV supplied through UNICEF has carried VVMs. Beginning in January 2001, all vaccines supplied by UNICEF were required to have VVMs. Implementation is moving forward particularly for vaccines procured through the Vaccine Fund. PATH and others are working toward resolution of issues with a few vaccine manufacturers yet unwilling to meet specifications.

Plans for the Next Six Months

- Assist the GAVI Secretariat and the designated developing-country manufacturers in the collection of data and presentation of a rationale for acceleration of the implementation process for the June board meeting of GAVI.
- Launch a project requested by the GAVI Task Force on Implementation to establish and evaluate a system of monitoring and reporting on vaccine wastage related to VVM status within the routine monthly reporting system.
- Monitor and assist with publication of VVM training materials at WHO and the integration of VVMs into other immunization training materials and documents.
- Opportunistically provide technical assistance to countries through CVP, HealthTech, and GAVI activities.

Vaccine Stabilization

Health Need Addressed

The cold chain is a complex system of personnel and equipment designed to ensure vaccine quality during distribution of vaccines from the manufacturer to the point of use. Costs associated with maintaining the refrigeration element of the cold chain in developing countries are estimated to be about US\$200 million annually. Much of the cold chain in developing countries is old and in disrepair or must be replaced due to new environmental regulations. Capacity demands are being placed on the system due to the introduction of new vaccines such as hepatitis B and *Haemophilus influenzae* type b (Hib). In addition to these issues, freezing of freeze-sensitive vaccines appears to be a frequent occurrence, resulting in certain but unquantified damage to these vaccines. Although much can be done in the short term to relieve pressure on the system, thermostable vaccines are needed to ensure quality of vaccines during storage and distribution and to decrease the logistical complexity, equipment, and costs associated with maintaining the cold chain. The ultimate result will be safer, more effective vaccines reaching more children.

HealthTech IV Solution and Potential Impact

Cryptobionts are a class of organisms that retain full metabolic activity following complete desiccation and rehydration. This unique characteristic permits these organisms to “preserve” themselves and survive in harsh environments that would otherwise produce damage. Specific sugars have been identified in these organisms that protect them from damage during desiccation. These sugars and other excipients have been used to dry protein, bacterial, and viral vaccines to achieve a glass-like state. In this state, molecular movement is halted, and degradation of the biological material does not occur.

From a practical standpoint, glassified vaccines have limitations since they must be either delivered dry through new administration routes or reconstituted prior to use at which point their heat stability characteristics (and cold chain requirements) are essentially the same as for current vaccines. Reconstitution is also risk-prone as safety is potentially compromised if the incorrect diluent is used or if safe injection practices are not followed during the reconstitution step or during withdrawal of doses. For these reasons, PATH under HealthTech and other programs is focusing efforts on technologies that avoid reconstitution. Immediate research efforts are geared toward glass-stabilized vaccine that is suspended in a nonaqueous liquid. This thermostable liquid can be delivered by standard or prefilled syringe and needle and introduced into immunization programs without changing current administration practices.

Milestones and Accomplishments Achieved in the Past Six Months

- The Bill & Melinda Gates Foundation has notified PATH of their intention to support the development of priority thermostable vaccines through a four-year grant. At the foundation’s request, PATH is revising the implementation plan to emphasize technology development for all EPI antigens and to more aggressively facilitate uptake of the technology.
- PATH and Cambridge Biostability Limited (CBL) formalized their agreement on terms that will ensure access for vaccine manufacturers to CBL’s composite-glass and non-aqueous suspension methods for use with vaccines destined for developing-country, public-sector immunization programs
- PATH developed and distributed a model, in collaboration with a consultant, to forecast demand for childhood vaccines used in public-sector, low- and middle-income countries from 2002 to

2014. The model brings together data from various sources to calculate vaccine demand per antigen per country. The purpose is to better understand the trends and projections for vaccines that will be needed by the public sector over the next twelve years and to help ensure that vaccines selected for stabilization will be of high priority to the public sector during this time frame and beyond. The model was intentionally designed with significant flexibility, as the information is likely to be useful for other applications as well. It was distributed to individuals who serve as key focal points for vaccine and vaccine-related technology supply issues in other organizations and has generated significant interest from the Bill & Melinda Gates Foundation, UNICEF, WHO, the Global Alliance for Vaccines and Immunization (GAVI) Financing Task Force, and The Vaccine Fund, as well as other vaccine initiatives, such as the International AIDS Vaccine Initiative (IAVI), Malaria Vaccine Initiative (MVI), and Meningitis Vaccine Project (MVP).

- PATH initiated a dialogue with a major holder of intellectual property in the area of sugar-glass stabilization, Quadrant Drug Delivery Limited. The original Quadrant owners recently bought back technology rights from Elan Corporation. Discussions are underway with Quadrant regarding possible mechanisms for securing access to their technologies for developing-country, public-sector vaccine applications.
- The New Technologies Working Group submitted a strategy document on vaccine stabilization to the GAVI Working Group (WG). The WG is using the document to develop final recommendations for submission to the GAVI Board in December 2003. The final recommendations are expected to be supportive of PATH's approach and work in this area.
- Agreement, in principle, was secured with Chiron Vaccines (Italy) to stabilize measles containing vaccines during a meeting in London with PATH and CBL representatives.
- Serum Institute of India (SII), PATH, and CBL have agreed to move forward with stabilization of SII's measles-containing and DTP vaccines.
- PATH introduced representatives of Injectile Technologies GmbH, producer of dissolvable needles, to CBL representatives so that consideration can be given to merging the technologies of the two companies to pursue sugar-glass needles.
- Research has been carried out to identify sources for perfluorocarbon liquids to be used as the suspension media for the stabilized vaccine. More than 30 companies have been approached, and two companies have been identified as lead candidates for initial procurement—Fluoromed, L.P. in Round Rock, TX and F2 Chemicals, Ltd in Lancashire, UK. Initial meetings were held with both companies. In addition, CBL met with a potential producer in China.

Problems Encountered and Actions Taken

- **Problem:** There are very few potential suppliers of high quality perfluorocarbon (PFC) liquids. No company currently supplies the PFCs in the required grade for clinical use.
Action: PATH will work with the identified candidates, F2 and Fluoromed. Custom product will be purchased for preclinical studies. If results are favorable, PATH will explore appropriate mechanisms to achieve adequate supply through agreements and/or joint investment.
- **Problem:** The sugar interference problem reported in the last HealthTech report that prevents stability studies of Hib vaccine provided by Panacea Biotech is still unresolved. The work requires purchase of a High Pressure Liquid Chromatography (HPLC) system with a special column that CBL cannot yet afford to purchase.

Action: Fundraising at CBL continues. PATH is considering a loan to CBL (via the PATH Loan Fund) so that purchase of this, and other equipment, can proceed. CBL plans a public offering in October 2003 that should yield funds by the end of the year.

- **Problem:** MVP has incurred some technical delays, meaning that they will not have vaccine available for stabilization until fall 2004.

Action: Follow up with the MVP in April 2004.

Status of Project as of September 2003

Significant funding has been secured that will result in an expanded team and scope of work. Initial feasibility work, carried out under HealthTech, shows promise for the project on several fronts.

Plans for the Next Six Months

- Public announcement of the grant from the Bill & Melinda Gates Foundation is expected during the fourth quarter of 2003.
- A signing ceremony will be conducted in the British House of Commons in November 2003 to celebrate and publicize the PATH/CBL agreement.
- Several key positions are expected to be filled over the next six months, among them a Technical Leader and Commercialization Officer.
- Stabilization of SII's and Chiron's measles-containing vaccines should be completed. The stabilized products will be sent to the respective producers for further testing.
- A laboratory method to prevent sugar interference will be completed by the end of 2003.
- Six-month hepatitis B and Hib vaccine stability results and PFC toxicology results will be available from Panacea Biotech (India). Plans will be made for a further round of stabilization and testing.
- Protocols for toxicology and safety testing will be designed and testing will be initiated with perfluorodecalin.
- A preliminary assessment of CBL technology will be conducted by a consultant to identify issues related to scale-up for pilot production and manufacture.
- PATH will continue to pursue options for access to intellectual property for use of this technology for public-sector vaccine applications.

Cold Chain Technologies

Health Need Addressed

Improperly maintained or outdated refrigeration equipment, poor compliance with cold chain procedures, inadequate monitoring, and poor understanding of the dangers of vaccine freezing contribute to the weakness of the current vaccine cold chain. Emphasis has long been placed on keeping vaccines cold, with less attention devoted to prevention of vaccine damage from freezing. Published reports and field evidence demonstrate that accidental freezing of vaccines in the cold chain is commonplace, potentially resulting in widespread delivery of vaccines whose potency has been compromised.

HealthTech IV Solution and Potential Impact

Cold chain technologies, such as the vaccine vial monitor (VVMs), new refrigeration technologies, and new vaccine presentations strengthen vaccination programs' ability to provide outreach services, improve the reliability of vaccine storage and transport, and reduce unnecessary wastage of valuable vaccines. Most importantly, these technologies will reduce the delivery of ineffective vaccines. Immediate priorities for an efficient and reliable cold chain are:

- Increase awareness of the consequences of freezing certain vaccines and expanded immunization outreach.
- Model flexible cold chain options that increase capacity for future vaccines and single-dose presentations.
- Improve cold chain reliability, performance, and affordability with new vaccine refrigeration and carrier technologies.



Supported by the USAID-funded HealthTech program, and in collaboration with other organizations, PATH is addressing these priorities. Efforts include fostering changes in cold chain policies and an improved global awareness of the magnitude of accidental vaccine freezing. Evaluation and development is directed toward new technologies which improve vaccine storage and transport, prevent accidental freezing, and increase cold chain capacity for important new vaccines and presentations.

Milestones and Accomplishments Achieved in the Past Six Months

- Completed field evaluations of VaxiCool ice-free refrigerator system in Mozambique and Indonesia, with the evaluation in Ukraine continuing through the winter months of 2003 to 2004.
- Completed a field monitoring study to identify cold chain freezing in Mozambique. Results to be circulated in 2004.
- Ongoing modeling of freeze-proof methods for vaccine distribution in Indonesia. Recently completed evaluation of an ice-free vaccine distribution system, which demonstrated that vaccine freezing can be reduced while still maintaining vaccine potency.

- Conducted laboratory testing of two different prototype freeze indicator devices. As a result of the study, one freeze indicator was recently approved by WHO and the other device recommended for further product development.
- Developed a set of eight educational and training posters to reinforce proper refrigeration, transport, and monitoring procedures. These materials have been translated into French and distributed to African regional cold chain managers. They were also used for training and distributed at a SEARO immunization conference. One was translated into Indonesian and local funding was obtained to print and distribute 8,000 posters, one to every health center in the country.
- Assisted in assessment of Vietnam and Cambodia vaccine cold chains. Poor vaccine storage conditions were identified in both countries, and a follow-on temperature monitoring study is planned in Vietnam for early 2004.
- Assisted in preparations for out-of-cold-chain, hepatitis B immunization study in China.
- Conducted laboratory testing of the solar power supply of the VaxiCool™* ice-free refrigeration and outreach system. Tests indicated further refinement of the solar power system is required. A consultant was hired to assist the manufacturer in system optimization.
- Developed a protocol and identified sites in Senegal and Indonesia for field testing of the SolarChill vaccine refrigerator. The SolarChill is a new solar refrigerator which utilizes ice storage rather than a battery, a frequent source of failure in solar systems, to maintain vaccine-safe temperatures during periods without adequate sunshine.
- Continued discussions and advocacy regarding freeze prevention equipment and studies with the Technology and Operations Panel (TOP).

Problems Encountered and Actions Taken

- **Problem:** VaxiCool was tested and found to need improvements in its solar charging control system.
Action: A consultant, Terry Hart of IT Power India, was hired to work with the manufacturer to optimize the component design.
- **Problem:** Policy makers, managers, and health workers are reluctant to alter standard cold chain practices.
Action: Developed a protocol called “Assessment of Freezing in the Cold Chain” to be used by countries to document the extent of accidental vaccine freezing in the cold chain. In addition, HealthTech will model out-of-cold-chain and options for a two-temperature cold chain to document safety and advantages of a more flexible cold chain policy. Also by promoting discussion amongst international cold chain experts and agencies, HealthTech hopes to facilitate consideration of and develop solutions to widespread accidental freezing.

Status of Project as of September 2003

- Several freeze-proof technologies and systems continue to be modeled and studied. Evidence is being collected to show their impact.

* VaxiCool is a trademark of Energy Storage Technologies, Inc.

Plans for the Next Six Months

- Collect and analyze data from the VaxiCool evaluations in Mozambique, Ukraine, and Indonesia in 2003.
- Conduct field evaluations of the SolarChill vaccine refrigerator in Indonesia and Senegal in 2004.
- Develop and test “freeze-proof” and “cool chain” technologies such as eutectic cold packs and new vaccine carrier designs.
- Collect further evidence of a two-temperature cold chain approach to prevent vaccine freezing and reduce distribution costs in Indonesia.
- Continue to collaborate with WHO, UNICEF, and vaccine manufacturers through TOP.
- Explore with WHO ways to accelerate the introduction of VVMs on all vaccines to facilitate the ability of countries to remove heat-stable vaccines from the cold chain.
- Publish the results of electronic temperature monitoring of the Indonesian cold chain in the *WHO Bulletin*.
- Assist countries in assessing freezing in the cold chain using the PATH-developed protocol.
- Model flexible cold chain policies in several countries. Work with WHO on a policy document on the “flexible cold chain” to assist countries with implementation.
- Facilitate distribution and use of PATH freeze-prevention materials among cold chain managers and decision makers worldwide.

Introduction of Injectable Contraceptives in the Uniject™ Device

Health Need Addressed

Injectable contraceptives are becoming increasingly popular around the globe as women search for safe, highly effective, reversible methods of contraception that do not require compliance with a daily regimen. Depot medroxyprogesterone acetate (DMPA) is administered by injection once every three months, making it highly convenient. Cyclofem®* (also known as Lunelle and CycloProvera) injectable contraceptive is administered by injection every month and is formulated to allow women to have more normal menstrual cycles—an advantage in many cultures. Currently, international development and family planning agencies purchase over 25 million doses of DMPA injectable contraceptives annually for distribution to family planning programs throughout developing countries. Approximately seven million doses of Cyclofem injectable contraceptives were sold in the year 2000.

International development and family planning agencies and recipient governments are continually looking for feasible and affordable methods to reduce unsafe injection practices that could lead to the spread of bloodborne diseases. Provision of one sterile needle and syringe with every dose of injectable contraceptive is the current standard. However, there is a risk with disposable syringes that they will be reused. Auto-disable (AD) syringes prevent reuse, but like disposable syringes they can be diverted to other uses during the distribution process. The Uniject™† prefill injection device has distinct advantages in terms of both safety and procurement.

HealthTech IV Solution and Potential Impact

A decade ago, prefilled syringes were too costly for use in public-sector health programs, and no prefilled syringe on the market offered an AD feature. Under the HealthTech project, PATH was able to develop the Uniject device, a proprietary, prefilled, AD injection system. The Uniject device prevents reuse, simplifies matching of syringes and supplies, ensures dose accuracy, and is so simple to use that injection at home by the patient or a family member is feasible. Now the device is being considered for use filled with injectable contraceptives. With funding from the USAID Office of Population, PATH has been working for a number of years with the dominant international supplier of DMPA injectable contraceptive to evaluate potential use of Uniject devices. This company was Pharmacia until it merged with Pfizer in April 2003. PATH has also worked with Aplicaciones Farmacéuticas (AF), a Mexican pharmaceutical company which has developed but not yet launched a version of its once-a-month injectable contraceptive, Cyclofem in Uniject devices.

Milestones and Accomplishments Achieved in the Past Six Months

- Reinitiated face-to-face discussions between USAID Office of Population, Pfizer, and PATH regarding opportunities and challenges in creating availability of the new formulation of DMPA in the Uniject device (hereafter called "DMPA-Uniject"). (Meeting at USAID in July 2003.)
- Pfizer team recommended that they plan to pursue final technical feasibility issues during late 2003 and early 2004. They have high confidence of technical success but do need to confirm that minor adjustments to the formulation of their new DMPA will enhance its stability in Uniject.

* Cyclofem is a registered trademark of the Concept Foundation.

† Uniject is a trademark of BD.

- Pfizer team should then make a proposal to their senior management in mid-2004 for investment in full-scale implementation of a new formulation DMPA-Uniject to serve USAID and other international donor needs.
- PATH and USAID agreed to provide information and support to the Pfizer team as requested and to follow up in Fall 2003.

Problems Encountered and Actions Taken

No significant problems encountered.

Status of Project as of September 2003

- Pfizer team is developing an internal plan to complete feasibility work and then propose full investment in new formulation DMPA-Uniject scale-up for production and distribution.
- DMPA-Uniject project has “survived” the Pharmacia merger into Pfizer (**many** Pharmacia products and development projects have been dropped!) and has clear, high-level support from Vice President Paul Richardson and a knowledgeable, committed project champion in Enrico Liggeri. After a long period of transition and uncertainty, the likelihood of project success (as measured by having Pfizer supply their new DMPA-Uniject) is increasing.
- AF has decided not to commercialize the product, so PATH is no longer working with them.

Plans for the Next Six Months

- PATH’s activities on this project continue to be extremely dependant on the pace and progress (or lack thereof) of Pfizer’s work. Until Pfizer makes its full commitment to invest in scale-up, production, and distribution of new formulation DMPA-Uniject, PATH will primarily facilitate communications, link for updates, and provide any program perspective, contact, or other analysis that can help strengthen their business case for this investment.

Gentamicin in Uniject™ Devices

Health Need Addressed

The WHO estimates that at least four million neonatal deaths (i.e., death during the first 28 days of life) occur around the world every year. Severe bacterial infections are major contributors of newborn morbidity and mortality. Each year, an estimated 30 million children born in the developing world develop an infection during the neonatal period, and infectious diseases account for over one-third of all neonatal deaths. In 2000, a WHO advisory committee recommended intramuscular injections of ampicillin and gentamicin as the standard therapy for these bacterial infections and the treatment of neonatal septicemia, meningitis, and pneumonia. Case-fatality rates for severe bacterial infections are high in part due to not administering or delaying the administration of necessary antibiotics. Therefore, it is important that newborns with these infections receive immediate treatment, even before the infectious agent is known. When neonatal infections occur, many deaths can be avoided if the signs are recognized early and the disease is treated promptly.

HealthTech IV Solution and Potential Impact

To improve neonatal survival from infectious diseases, Uniject™* injection devices prefilled with a single gentamicin dose (hereafter called “gentamicin-Uniject”) could be easily transported and used in a home setting with an oral antibiotic when the signs of a neonatal infection are first detected. Community-based health workers could be trained to use the gentamicin-Uniject device and a complementary oral antibiotic in order to extend the accessibility and facilitate the administration of antibiotics for early treatment of neonatal infections. Furthermore, gentamicin-Uniject devices could potentially be incorporated into the revised integrated management of childhood illness (IMCI) guidelines, which have been adapted for acute management of common infectious neonatal illnesses. If the gentamicin-Uniject device is used safely, properly, and efficiently for infants with severe bacterial infections, Uniject devices could make a significant contribution to reducing neonatal mortality in developing countries. HealthTech has recently allocated funds for further development of this application of the Uniject device, but meanwhile the following activities have been undertaken under cofunding from the Bill & Melinda Gates Foundation.

Milestones and Accomplishments Achieved in the Past Six Months

- The project team has been reconfigured to focus on generating an adequate supply of Uniject products by working directly with select pharmaceutical manufacturers to build capacity and skill in filling and producing Uniject devices. The need for technical assistance and the complexity of the undertaking is far greater than originally anticipated.
- Draft budget, scope of work, and subcontract are under negotiation with Dolphin Laboratories Limited for the production of gentamicin-Uniject devices (as well as oxytocin in the Uniject device (hereafter called “oxytocin-Uniject”) for use in field trial evaluations.
- Studies were completed in India and Bangladesh to verify a safe and effective dosage for once-daily gentamicin-Uniject in neonates. The Data and Safety Monitoring Board (DSMB) concluded that the objectives for the pharmacokinetic testing of gentamicin, as the first step in development of the gentamicin-Uniject device, have been met. The following dosages are now recommended for use in the Uniject device: 13.5 mg q 24 h for patients \geq 2500 g, 10 mg q 24 h for patients 2000 to 2499 g, and 10 mg q 48 h for patients $<$ 2000 g. However, final

* Uniject is a trademark of BD.

recommendations for use of these dosages is pending until the results of hearing tests on the study patients are available. It was recommended that enrollment into the pharmacokinetic study be stopped at all the sites, and that all study subjects undergo follow-up hearing testing as planned.

- A plan has been developed for the implementation of the evaluation of the Uniject device in an existing field study on gentamicin for newborns in collaboration with Save the Children. The study will be nested within a larger neonatal health demonstration project in Sylhet, with the gentamicin-Uniject intervention beginning around March 2004, assuming that the product is ready to go at that time. If not, alternative sites are available in India or Pakistan.

Problems Encountered and Actions Taken

- **Problem:** Delay of transfer of machine and fill of product has delayed other milestones. The need for substantial technical assistance to Dolphin Laboratories Ltd. to support and plan for the manufacture of the Uniject product has been greater than anticipated.

Action: Clear communication via teleconference and site visits by PATH India staff has enabled progress to be made toward transferring the machine and coordinating the fill.

- **Problem:** Delay in manufacture of product will delay the start of field evaluation; if delay extends past March 2004, the opportunity for the current collaboration with Save the Children: The Saving Newborn Lives Initiative (SNL) will likely be missed.

Action: Regular communication with SNL collaborators regarding status of product manufacture. SNL staff believe that they will be able to integrate the sub-study into the parent study within the March 2004 time frame.

Status of Project as of September 2003

Dose verification studies indicate favorable results. Planning is underway for transfer of Horizon filling machine to Dolphin Laboratories Ltd. in India to fill product for stability testing and eventual use in field evaluation trials.

Plans for the Next Six Months

- Arrange for donation of Horizon Uniject filling machine to PATH. Coordinate transfer of Horizon Uniject filling machine from BD/France to Dolphin Laboratories Ltd. in India.
- Facilitate installation of Horizon machine by sending consultant to assist with quality assurance procedures and media fills.
- Conduct compatibility testing of gentamicin-Uniject at Dolphin R&D laboratory in India during period that the Horizon machine is being transferred to Dolphin Laboratories Limited.
- Given favorable results from compatibility testing, have Dolphin conduct fill of gentamicin-and Oxytocin-Uniject products for stability testing and use in field evaluation.
- Negotiate Scope of Work and subcontract with SNL for implementation of field trial in Bangladesh.
- Seek ethical approvals from PATH, Johns Hopkins University, and local institutions for implementation of field trial research protocol.

Mass Campaign Jet Injector

Health Need Addressed

With the advent of the AIDS epidemic and a clearer understanding of the transmission of hepatitis B and other bloodborne diseases through the use of unsafe needles worldwide, safe-injection technologies have become a high priority for international health agencies. Estimates indicate that more than 50 percent of developing-country injections are unsafe. Reuse of contaminated syringes, needle-stick injuries among health workers, and threats to the community from improperly disposed of and contaminated sharps and needles present serious health risks. Multi-dose jet injectors, although credited with decades of use in the field, are no longer used due to evidence of cross contamination between injections. The availability of a safe and contamination-free multi-dose jet injector would have great beneficial impact on public health worldwide.

HealthTech IV Solution and Potential Impact

Under the HealthTech program, PATH has partnered with Felton, International (Felton) of Kansas, in the evaluation, testing, and design refinement of a new generation, multi-dose jet injector. This is a high-workload injector (designated the BI-100) which is intended for use in mass immunization campaigns. The design of the injector involves a novel and effective approach (a disposable shield between the nozzle and the site of injection) to eliminate cross contamination between injections while maintaining a high rate of vaccine delivery to multiple patients.

This technology could provide significant improvements in the safety, efficiency, and effectiveness of immunization programs. In particular, this device would be invaluable in providing the necessary immunization coverage required to eliminate measles worldwide. Both immunization campaigns and health clinics would benefit from the use of this device through increased safety and reduced costs.

Milestones and Accomplishments Achieved in the Past Six Months

- Completed and signed the Collaborative Research, Development, and License Agreement dated April 11, 2003, between Felton International and PATH.
- Presented latest jet injector design at Measles Steering Committee Meeting April 29 to 30 at WHO in Geneva. Positive response was generated, technology was recognized as being on a faster track towards field introduction and market use if safety testing could be conducted.
- Conducted prototype build and testing of current injector design (protector cap and injector). Results of performance testing indicated the need for further design development to meet requirements of design.
- Identified and implemented additional design changes, working closely with Felton International.
- Collaborated with WHO in the planning of validation studies of current protocols for hepatitis B PCR (polymerase chain reaction) and HSA (human serum albumin) ELISA detection methods that will be used to test the final design and allow for reversal of the WHO policy.
- Held discussions with hepatitis B experts in the United States in order to identify a suitable study site for a hepatitis B safety trial (ongoing).
- Working in collaboration with WHO, drafted clinical testing protocol for safety trial, which will serve as a basis for planned hepatitis B and HSA safety testing.

- Completion of a cost model implemented by Instituto Nacional de Salud Pública, which demonstrates the cost-effectiveness and impact of the jet injector in mass immunization campaigns compared to the use of auto-disable syringes. This model will be used for future jet injector introduction activities, introducing modification of the cost model to address specific country and program needs.
- Received a major grant from the Bill & Melinda Gates Foundation which will allow PATH to speed up the development, safety testing, and introduction of the device. The work plan is contingent on reaching a new scope of work and modified collaboration agreement terms with Felton International.

Problems Encountered and Actions Taken

Business Status of Felton International

- **Problem:** Felton has continued to face challenges in obtaining adequate investment and funding for the development of a human injector for mass immunizations in the developing world. Unexpected losses from sales of their jet injectors for animals have aggravated the situation. These shortfalls have caused significant delays in implementation—Felton has not been able to complete the design and development of the injector as originally agreed.

Action: PATH has provided an offer to Felton that would involve PATH assuming the role of completing the design and development of the mass campaign jet injector in an effort to relieve Felton of this resource and financial burden. To date Felton has rejected the offers made by PATH; Felton is concerned about dilution of their intellectual property ownership. Negotiations are continuing.

International Health Community Acceptance of the Methodology for Human Safety Testing

- **Problem:** Consensus as to a target level of detection for any assay methodology to be used for human safety testing is still a matter of discussion and debate.

Action: PATH is recommending a more practical approach to determine an appropriate limit of detection for jet injector safety testing. This approach involves comparing current standards of practice for donated blood screening for hepatitis B with the achievable limits of detection for assays identified for jet injector safety testing. It is proposed that planned hepatitis B safety testing include an assay comparison in order to establish a practical baseline for use of the HSA ELISA assay for large-scale, WHO safety testing.

Status of Project as of September 2003

Development of the device continues while issues related to the roles played by PATH and Felton in the project as well as intellectual property are worked out.

Plans for the Next Six Months

Under a new scope of work and understanding with Felton International, the Mass Campaign Jet Injector team at PATH plans to continue and complete design and development of the injector in order to allow for human clinical evaluation during first quarter 2004. Additionally PATH will work with WHO to finalize plans for safety testing in order to allow for reversal of WHO policy by the end of 2004. PATH plans to conduct this work under new funding from the Bill & Melinda Gates Foundation.

Overview of planned milestones:

- Complete design and development of Mass Campaign Jet Injector.
- Conduct validation activities for both AMS and hepatitis B detection assays.
- Conduct hepatitis B safety trial with jet injector prototypes.
- Establish practical baseline limit of detection for HSA assay to be used in WHO safety testing.
- Work with the WHO advisory group on human safety testing of the injector.
- Coordinate with policy makers in the international public health community to promote acceptance of the Mass Campaign Jet Injector.

Safe Medical Waste

Health Need Addressed

Each year, more than 16 billion injections are administered worldwide. Concerns about injection safety, primarily through reuse of syringes, have become a major public health priority. Estimates indicate that more than 50 percent of injections in developing countries are unsafe (WHO Injection Safety, Quality of Immunization Services, August 28, 1998). Unsafe injections account for 33 percent of new hepatitis B infections, 42 percent of new hepatitis C infections, and 2 percent of new HIV infections (WHO, Safe Injection Global Network, Injection Safety. WHO/BCT/DCT/01.3. 2001). The main tool to prevent reuse of non-sterile syringes and needles is use of auto-disable (AD) injection devices. Procurement of AD syringes is mandated by WHO, UNICEF, and GAVI for their immunization programs.

Appropriate sharps and syringe disposal also play a role in safe injection. It is important that waste not be dangerous for the community, and that people be protected from hazards when collecting, handling, storing, transporting, treating, or disposing of waste. With estimates of 700 million AD syringes being procured by 2005 for global immunization programs alone, the volume of contaminated sharps waste will grow, and safe disposal therefore becomes increasingly important. Improper disposal of such syringe waste presents a serious risk to the medical waste disposal workers and to the community at large.

HealthTech IV Solution and Potential Impact

There is an immediate need for a needle disposal system that is simple, inexpensive, and requires minimal handling of the contaminated needles by health care workers and waste disposal personnel. Point-of-use needle removal and subsequent needle containment provide immediate isolation of contaminated sharps, decrease the required volume of disposal boxes or containers, can aid in discouraging reuse of non-AD syringes, and increase syringe disposal options.

Any situation in which a needle and syringe are used is an appropriate setting for point-of-use needle removal and disposal. This technology would improve safe disposal for large-scale immunization campaigns as well as for routine immunization and smaller outreach clinics. A needle remover must fit into the existing settings in which it will be used, and into those settings' existing waste disposal systems—for example burial, incineration, or plastic reprocessing. Urban low- to medium-infrastructure health centers pose a significant challenge for on-site processing of sharps waste because of the larger volumes of waste, the lack of space for burying, and the economic or environmental constraints prohibiting incineration.

HealthTech is continuing to work with commercial manufacturers and developers of needle removers (Bio Medical Operations Australia, Micronics (US), and Allan Medical Safety) to optimize their devices for developing-country populations. We are evaluating needle removal in developing countries to show how the device benefits sharps waste disposal systems. We have made the design of the PATH-designed needle remover prototype available to commercial manufacturers. We are working with WHO globally to develop specifications and policy guidance about needle removers so that the devices can be more widely purchased and used.

Milestones and Accomplishments Achieved in the Past Six Months

- PATH continued the needle remover demonstration project in India scheduled to end in November 2003. Nine sites in Delhi and Jaipur, including two control sites, are participating. This demonstration project will document the performance, acceptability, and effect of needle removers on immunization waste management practices. Data are being gathered on device durability, reliability, ease of use, waste volumes, needle disposal practices, syringe disposal practices, and needle-stick injury. By September, data were collected on more than 5,000 person-days of use, with more than 34,000 needles removed in both static and outreach settings. The results will be used to change global guidance on used needle and syringe disposal in immunization programs.
- PATH adapted its India protocol to make it generic so that other sponsors could apply it to evaluations in other countries. WHO is using the protocol in a needle remover evaluation in Eritrea, scheduled to begin in October 2003.
- PATH developed and distributed a design package to solicit interest from commercial manufacturers for the HealthTech-designed needle remover (see picture). Within one year's time, the package will be disclosed in the public domain for any other groups that are interested.
- PATH organized a workshop in July in Indonesia to present the national policy on sharps waste management in primary health facilities to provincial immunization managers and to demonstrate technical solutions for sharps disposal. The workshop was significant in that it raised awareness of issues of operation, community acceptance, syringe collection and transportation systems, responsibility, and budget. This work will continue under PATH's Children's Vaccine Program with support from the HealthTech Sharps Solutions team.
- PATH initiated bench investigation in needle disposal for settings where it is not possible to dig protected needle pits. This investigation will provide another solution for urban sharps disposal where disposal options are limited.



One of the devices PATH is evaluating in India.

Problems Encountered and Actions Taken

- **Problem:** One of the two devices intended for evaluation in India did not function consistently with non-auto-disable (AD) syringes.
Action: Since all of the syringes in Delhi are non-AD, we removed this device from the Delhi sites and substituted a third needle remover.
- **Problem:** Our original strategy had been to license the PATH-developed needle remover to a company for production and distribution. Due to the device simplicity, however, we determined that a patent would not be granted or difficult to defend. In addition, the device design is not yet optimized for mass production and still requires significant design inputs to make the prototype appropriate for molding. For these reasons, we felt that a licensing strategy would not be successful.

Action: We implemented an alternative strategy to disclose the “as is” design package to all companies currently producing and selling syringes to public-sector immunization programs or currently producing and selling sharps waste disposal products to public-sector immunization programs. Based on the responses received, we will then determine level of interest and need for additional HealthTech inputs to convert the design for production.

- **Problem:** Multiple systems will be required for the safe handling and disposal of needles after they have been separated from the syringes. For example, underground protected needle pits are not feasible in some settings due to a lack of land or a high water table.

Action: PATH’s investigation of alternative needle-disposal options in urban settings is aimed at finding another solution for sharps disposal.

Status of Project as of September 2003

Evaluation of needle remover use in India is ongoing. Urban needle disposal options are under investigation. The PATH needle remover design package is available to commercial companies.

Plans for the Next Six Months

- Complete needle remover demonstration project in India; analyze and disseminate results.
- Assist with needle remover demonstration project in Indonesia.
- Continue to network with existing manufacturers and immunization program managers to connect programs with appropriate needle-removal devices.
- Publish the design package of the HealthTech-designed needle remover for outreach on the WHO health care waste web site and SIGN so that it will be in the public domain and therefore available to manufacturers throughout the world.
- Initiate a field evaluation of a new urban disposal solution in field setting.

Retinol Binding Protein Enzyme Immunoassay (RBP-EIA)

Health Need Addressed

For almost 50 years, researchers have known that administering oral doses of vitamin A could prevent consequences of severe vitamin A deficiency (VAD)—including blindness and death. More recently, studies to evaluate the efficacy of Vitamin A supplementation among preschool children, ages six months to five years, from several countries where VAD is endemic have indicated that almost one-quarter of early childhood deaths could be prevented by ensuring that children receive high-dose vitamin A supplements. In addition, efforts to improve the vitamin A intake through fortification of commonly consumed staple foods and condiments have been implemented in many countries. Public health planners and researchers need easier, less expensive ways to assess the extent of VAD among populations to inform public policies and promote well-targeted vitamin A intervention programs.

VAD is a significant public health problem in many developing countries, with the most vulnerable groups being preschool children and lactating and pregnant women. Vitamin A needs increase during lactation so additional intake is required to replace daily losses in breast milk. * In children, VAD is the leading cause of preventable visual impairment and blindness. On a global basis, an estimated 250,000 to 500,000 VAD children become blind each year, and about half of them die within a year of becoming blind.†

In order to identify the optimal mix of strategies to combat VAD and to monitor progress in interventions, it is essential to have reliable epidemiological information on the magnitude and distribution of VAD in populations. The current tools employed are expensive and require external assistance; simpler, less-expensive, field-appropriate tools are necessary.

HealthTech IV Solution and Potential Impact

The RBP-EIA was developed under the HealthTech program as a rapid, inexpensive test to measure the RBP concentration in serum specimens and has been found to serve as a surrogate marker for retinol. The RBP-EIA is intended for use as a population-based indicator of vitamin A status and to estimate the prevalence of VAD. This test has been designed to: produce data rapidly; reduce reliance on costly, centralized laboratory facilities; and provide an effective tool for field monitoring and recognition of VAD in at-risk populations. Results can be available within 35 to 40 minutes from the time that specimens are processed. The RBP-EIA can be used in laboratories at the provincial or district level by trained laboratory personnel who are proficient at performing routine ELISA tests.

Milestones and Accomplishments Achieved in the Past Six Months

Technical and Introduction Activities

- Analyzed baseline data (for RBP) from sera collected as part of a study in Tanzania. HPLC analysis of retinol from this panel of sera has recently been completed in a laboratory in Switzerland, and collaborators at the London School of Tropical Medicine are compiling the data. Once this has been completed, these data will be analyzed to further demonstrate the validation of RBP as a surrogate indicator of Vitamin A status.

* WHO/NUT/96.10.

† Sommer A. and West K. Vitamin A Deficiency. Health Survival and Vision. New York:Oxford University Press, 1996, Pp. 1-19 and 27-55.

- Analyzed the RBP content from matched sera and capillary blood (stored as dried blood spots [DBS]), collected as part of a maternal antenatal supplementation project in Guinea Bissau. Collaborators in the Department of Human Nutrition from the Royal Veterinary and Agricultural University, Denmark, had earlier analyzed data on the retinol concentration from the sera samples from this panel. Only 89 out of 1,200 samples of capillary blood stored as DBS were adequate for analysis. The data did not provide a strong correlation between RBP from sera and RBP from DBS because there was insufficient volume in the DBS samples. However sera were used to evaluate the correspondence between RBP and retinol, and the analysis showed a good correspondence between the two.
- Received archived DBS samples from Johns Hopkins University (JHU) from a panel of specimens that had been collected in Nepal. These will be analyzed for their RBP concentration and then compared to retinol that had been analyzed earlier from sera (by HPLC). It is expected that these analyses will help to confirm the feasibility of using DBS specimens collected from capillary blood by finger puncture as a biological sample for use with the RBP-EIA.
- Completed analysis of cost structure of PATH's RBP-EIA.
- Validation article accepted for publication in the American Journal of Clinical Nutrition titled, "Development of a rapid enzyme immunoassay for the detection of retinol binding protein."

Building Consensus

- Finalized the document "RBP-EIA: A New Approach to Assessing Vitamin A Deficiency" which can be used as advocacy for all stakeholder groups on the use of VAD testing for policy and program development and on the appropriate use of the RBP-EIA.
- Developed proposal with Wageningen University to explore activities related to ensuring the proper use of the RBP-EIA in laboratories in developing countries. Discussions with Wageningen University, Netherlands, are still underway to identify how Wageningen and PATH can most effectively collaborate to ensure proper use of the RPB-EIA.
- Completed report on the "Evaluation of Dilution Effects on the Retinol Binding Protein Enzyme Immunoassay," prepared in response to meetings held between PATH and the MOST project. This experiment was carried out to determine whether the linear range of the RBP could be extended by changing the dilution used for samples with high RBP concentrations. However, we found that there was no improvement in the precision of the test when varying the dilution concentration.

Commercialization.

- Obtained University of Massachusetts approval on licensing terms proposed to Scimedx, PATH's commercial collaborator, then executed a license agreement for the RBP-EIA technology with Scimedx in June 2003.
- Transferred technology to Scimedx in June 2003. Development of a prototype for scale-up began thereafter. Scimedx successfully produced a RBP-EIA prototype based on original standard operating procedures (SOP).

Problems Encountered and Actions Taken

- **Problem:** MOST has indicated that the RBP-EIA would be most useful if it could characterize the complete distribution of the VA status of a population, rather than serve as a test to establish prevalence estimates of VAD.

Action: PATH conducted a series of experiments to examine the effects of dilution of specimens whose RBP concentrations were above 20 µg RBP/ml by 1:50 (rather than 1:25 as has been optimized in the tests development. These experiments did not provide any improvement in precision beyond that already achieved with the original formulation. Consequently, we have recommended that the test be recognized for its performance as a critical tool that will facilitate VA assessment in the field.

- **Problem:** As part of the technology transfer to Scimedx, PATH and Scimedx have been carrying out experiments to identify potential cost-saving substitutes for the test components. Some technical difficulties have been encountered with demonstrating that minor changes in formulations do not interfere with the assay's ability to perform accurately.

Action: PATH and Scimedx are working together to conduct laboratory experiments and to finalize the test.

- **Problem:** PATH has expected to collaborate with Helen Keller Worldwide in Indonesia to analyze 2,000 serum and capillary-DBS samples taken from 1,000 mothers and 1,000 children. The trip has been postponed for security reasons.

Action: Once all the logistical arrangements for this trip can be coordinated within Indonesia, the validation exercise is expected to take place.

Status of Project as of September 2003

Initial laboratory and field validation of RBP-EIA is complete. The RBP-EIA technology has been transferred to Scimedx. Additional validations to look at RBP-EIA using DBS are continuing, and activities to ensure proper use in the field are being developed.

Plans for the Next Six Months

Technical and Introduction Activities

- Complete data analysis of DBS stability study conducted in Tanzania.
- Analyze RBP from serum collected as part of the follow-up enumeration for a micronutrient intervention research project being conducted in Senegal. Serum samples that were collected prior to the implementation of the intervention were already analyzed for their RBP content in March 2003. Sera from both the baseline and the follow-up will be subjected to analysis by HPLC for retinol. In addition to an assessment of the correspondence between RBP and retinol at each point in time, this study will provide an opportunity to assess the sensitivity of RBP to detect acute changes in Vitamin A status that may have resulted from exposure to an intervention.
- Analyze archived DBS samples provided by JHU to compare RBP from DBS with retinol analyzed from sera collected from pregnant and lactating women participating in the NNIPS trial in Nepal. We will also explore obtaining additional specimens from JHU's archive of DBS from their Nepal and Bangladesh studies. JHU already has analyzed serum retinol from these specimens.
- PATH staff will travel to Indonesia to conduct further analysis of a panel of matched sera and capillary DBS (collected in Cambodia). This work will help further validate the RBP-EIA and establish the feasibility of using DBS as a specimen with the RBP-EIA. The panel of sera from this population has already been analyzed for its retinol concentration and taken together with the RBP results from both sera and DBS will provide a unique opportunity to assess the

correspondence between the two parameters of VA status as measured from distinct biological specimen types. The Cambodia panel has also been analyzed for different indicators of chronic and acute inflammation, allowing for an evaluation of the potential impact that inflammation may have on VA status.

- Continue the promotion of an "early adopters" program to promote the introduction and appropriate use of the technology.
- Identify strategy and specific activities to ensure proper use of the test in laboratories in developing countries.

Building Consensus

- Explore a possible collaboration with a WHO-funded vitamin A intervention project in Malawi based at the HIV/AIDS treatment facility in the teaching hospital in Blantyre.
- Explore possible collaboration with UNICEF and CDC's IMMPaCt project for upcoming vitamin A assessment studies.
- Travel to provide an orientation to the RBP-EIA and discuss the tests use in operational research studies with faculty and students in the Department of Nutrition, University of California, Davis.

Commercialization

- First commercial lots to be ready from Scimedx for quality assurance evaluation by PATH in Fall 2003.
- First commercial product anticipated for early 2004.

Immunochromatographic Strip Test for Tuberculosis

Health Need Addressed

Tuberculosis (TB), a bacterial disease caused by *Mycobacterium tuberculosis*, is a major health problem in the developing world; its high prevalence in some countries is associated with immunosuppression due to HIV infections and AIDS. It is also a disease that is reemerging as a major health threat in the developed world. WHO statistics indicate that there are 20 million cases of active TB worldwide, and approximately 8 million new cases occur each year. TB has the highest mortality rate of any infectious disease in the world and results in approximately three million deaths annually. It is a highly contagious disease that can be difficult to accurately identify and diagnose. Because TB is curable with a course of antibiotic therapy, early diagnosis and treatment can curtail the spread of the disease within the general population.

HealthTech IV Solution and Potential Impact

The immunochromatographic strip (ICS) test for TB, developed during HealthTech III, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify specific serum antibodies to recombinant proteins specific for *Mycobacterium tuberculosis*. The test can be completed in 15 to 20 minutes and may be performed by technicians with minimal training. It can be performed directly on blood, serum, or plasma samples from patients in rural or smaller clinics or hospitals in the developing world, as well as in resource-limited settings. Accurate results can be returned within the same hour or day, allowing for more effective patient follow-up and counseling. The test also has potential use in the United States, Canada, and Eastern Europe, where TB is increasing among medically underserved populations.

Milestones and Accomplishments Achieved in the Past Six Months

- Data from the adult TB study in Botswana was presented as a poster at the American Thoracic Society meeting in May 2003 and has been accepted for publication in the *Journal of Infectious Diseases*.
- Final analysis of clinical data from a prospective field evaluation conducted in Ukraine has been completed. The sensitivity and specificity of the test in this population is 74.7 percent and 64.8 percent, respectively, when compared to AFB culture. The high false positive rate of the TB ICS test is surprising, since this has not been observed in other studies, and analysis is ongoing to identify the factors that may have contributed to this high false positive rate. Serum samples collected during this study have been shipped to PATH for assessment of other rapid tests.
- Although not funded under HealthTech, the PATH TB ICS team is collaborating with the CDC to further assess the performance of our TB ICS test, in addition to several other serological tests, in a pediatric population in Botswana. Data from this study is expected in early 2004.
- PATH has assessed the performance of a rapid serological test developed by Orchid Biomedical systems (Goa, India) using the sera collected in Ukraine. This test had a sensitivity and specificity of 61.1 percent and 48.3 percent, respectively. Again this data was surprising, as the test has been shown to have satisfactory performance with sera collected from Indian patients.
- Completed data enrollment forms from the prospective field evaluation at the Christian Medical College (CMC) in Vellore, India, have been entered into the Epi-info database.

Problems Encountered and Actions Taken

- **Problem:** Enrollment of patients at the CMC has continued to be a significant problem. As a result, Human Subjects Protection Committee (HSPC) approval for this study has expired and an updated protocol was submitted to PATH's HSPC in order to extend the enrollment period so that the study can be completed.
Action: HSPC approval has now been obtained in order to extend the evaluation, and staff at the PATH India office are contacting the CMC staff on a regular basis to reiterate that the study needs to be completed in a timely manner.
- **Problem:** Data from the Ukraine prospective study suggests that the specificity of our test is somewhat compromised in this patient population and raises some concerns on the suitability of the Corixa antigens used in our test for active case detection.
Action: Complete the analysis of the Ukraine study data to better understand the factors contributing to the high false positive rate.

Status of Project as of September 2003

At the present time the project is on hold pending receipt of the outstanding clinical report forms from the CMC. The team is exploring the feasibility of alternative technologies for active case detection.

Plans for the Next Six Months

- Complete patient enrollment at CMC in order to complete the study and conduct final analyses of data from the India and Ukraine sites.
- Convene a meeting with USAID and TB experts to discuss the data generated in the three prospective field trials. This meeting will assist the team in deciding whether to continue research and development activities on a serological test suitable for use in HIV-prevalent populations and to discuss the utility of the current test in HIV-negative populations.
- Meet with USAID to define and develop the scope of work for the PATH TB team for the next year.

Immunochromatographic Strip Test for Gonorrhea

Health Need Addressed

Despite long-standing, global public health efforts to control sexually transmitted diseases (STDs), infections caused by *Neisseria gonorrhoeae* still occur in epidemic proportions in the developing world and in specific regions of the United States. For effective control of gonorrhea (GC), STD-control programs must offer early and accurate diagnosis of symptomatic infection and identification of invasive, complicated, or asymptomatic infections. Control of STDs is also considered to be an essential component in the control of HIV/AIDS transmission.

HealthTech IV Solution and Potential Impact

The immunochromatographic ICS test for diagnosis of GC, developed under HealthTech III and IV, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify L7/L12, a specific gonococcal antigen, directly from clinical specimens. The strips are stable at ambient temperatures when packaged appropriately. This simple, rapid test will allow testing to be performed on direct clinical specimens from patients in rural or smaller clinics, regional hospitals and STD clinics in the developing world, or in other resource-limited settings. Results can be returned within one hour, thereby allowing effective patient follow-up, additional counseling, and prescription of therapeutic drugs, if needed. Epidemiological surveillance teams in the field may also use the test to gather baseline data or to assess the effect of public-health interventions.



Negative GC ICS

Milestones and Accomplishments Achieved in the Past Six Months

- Results from the development process and a prospective field evaluation of the GC ICS test in Johannesburg, South Africa, were presented at the International Society for Sexually Transmitted Diseases Research conference in Ottawa, Canada. This field evaluation was significant because the results suggest that vaginal exudates can be effectively used as specimens, which are easier to obtain and much less invasive compared with the standard method of collecting cervical swabs for GC testing.
- GC ICS test kits have been shipped to Benin for WHO's Sexually Transmitted Diseases Diagnostics Initiative (SDI) field evaluations. This multi-site trial, entitled "Clinic-based evaluation of rapid tests for the diagnosis of gonococcal infections," will provide field validation data from several thousand women in a "multi-round" format. Feedback about the performance of the test will then be sent to PATH, where the design of the test can be improved if necessary. A new generation of the test will then be sent back to the field for further clinical validation trials.
- A feasibility study of the utility of the GC ICS test for diagnosis and immediate treatment of GC in pharmacy settings in Kenya and Cambodia has been initiated. PATH Seattle, Kenya, and Cambodia staff already engaged in pharmacy studies for distribution of contraception in pharmacies are collaborating. Specifically, PATH is interested in the potential capacity of pharmacies to be distribution points for the test and to carry out sample collection, testing, diagnosis, and treatment, especially for men.

- Preliminary negotiations are underway with collaborators for an introduction study in South Africa that will involve operations research, acceptability of the test to users (health care workers) and end beneficiaries (men and women attending clinics), and assessments of cost-effectiveness of this new test.
- Options for license agreements with Orchid Biomedical (Goa, India), a commercial manufacturer, and Thermo Electron (Boulder, CO), the sole licensee of the monoclonal antibody reagent used in the tests, to transfer the manufacturing technology for the GC ICS test are being considered. Orchid and Thermo are reputable manufacturers and Orchid has been the recipient of PATH diagnostic technology in the past.

Problems Encountered and Actions Taken

- **Problem:** The production of test kits needed for the WHO trial took longer than expected.
Action: Laboratory and programmatic staff at PATH refined and further systematized the production process, so the delay in delivering the tests was minimized.

Status of Project as of September 2003

Prospective field evaluations, introduction and feasibility studies, and negotiations with commercial partners for a technology transfer agreement for the GC ICS test project are currently underway. Operating procedures are being developed for exploratory experiments in an effort to enhance the sensitivity of the test through several signal enhancement mechanisms.

Plans for the Next Six Months

- Send GC ICS test kits to a clinical site in India for a WHO-sponsored, multi-site field trial.
- Complete a manuscript focused on the results from the field validation trial in South Africa and submit to a peer-reviewed journal.
- Finalize technology transfer agreements between PATH, Orchid, and Thermo.
- Create an introduction study protocol along with collaborative agreements with participating institutions. PATH staff will travel to field sites to meet with collaborators and to hopefully begin data collection.
- Analyze results from the feasibility study in pharmacies and use them to inform a second round of data collection in Kenya and Cambodia.

Immunochromatographic Strip Test for Chlamydia

Health Need Addressed

As previously mentioned in the gonorrhea update, accurate diagnosis and control of STDs continues to be a challenge for health care providers in many developing countries. Although there are many simple and rapid tests available for the diagnosis of *Chlamydia trachomatis* (CT) infection, the sensitivity of many are low, and most, if not all, are too expensive for use in developing countries. The development of a rapid immunochromatographic strip (ICS) test for *Chlamydia* that is sufficiently sensitive, specific, rapid, and affordable would be an extremely valuable tool.

HealthTech IV Solution and Potential Impact

The ICS test for *Chlamydia*, developed under HealthTech III, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify a *Chlamydia*-specific antigen obtained directly from clinical specimens. The strips are stable at ambient temperatures if packaged appropriately. This simple, rapid test will allow testing to be performed on direct clinical specimens from patients at the point of care in rural or smaller clinics, hospitals in the developing world, or other resource-limited settings. Results can be returned within one hour, thereby allowing effective patient follow-up, additional counseling, and the prescribing of appropriate therapeutic drugs if needed. Epidemiological surveillance teams in the field may also use the test to gather baseline data or to assess the effect of public-health interventions.

Milestones and Accomplishments Achieved in the Past Six Months

- A protocol for collection of clinical specimens (vaginal, cervical, and discard cervical swabs) was written and PATH's Human Subjects Protection Committee approval was granted.
- Patient enrollment and sample collection were initiated at the participating clinics of Planned Parenthood Mar Monte in Northern California.
- The first set of samples (n=147 patients) was received at PATH. The samples are currently stored at -70°C until the number of specimens that are needed to initiate an evaluation are received. Clinical report forms indicate a CT prevalence of approximately 4.8 percent.
- Documents describing the processes and procedures for manufacturing the assay and its components (e.g. standard operating procedures.) are being drafted.

Problems Encountered and Actions Taken

- **Problem:** Collection of clinical specimens has been slower than anticipated.
Action: The slow collection of clinical specimens can be attributed to the collection start-up period as well as poor recruiting. The clinical sites have retrained their staff in recruiting patients, and recruitment efforts are being focused toward high-prevalence clinics. Collection rates and CT prevalence are therefore anticipated to increase. The situation is being monitored closely. Should collection of clinical specimens remain slow, alternative collection sites will be considered.

Status of Project as of September 2003

Development of the CT ICS test has slowed awaiting clinical samples. The clinical samples will be used to verify the clinical utility of the antibody selected for use in the assay. Further development work will be driven by the results of the antibody verification.

Plans for the Next Six Months

- Retrospective evaluation of clinical samples and assay verification will begin once the final prototype device is determined and specimens are available. This activity is anticipated to commence within the next six months.
- Development of the CT ICS test will continue once the assay reagents and components are verified with the retrospective evaluation.
- Documents describing the processes and procedures for manufacturing the assay and its components (e.g. standard operating procedures) will continue to be drafted and refined as the product is developed.

Immunochromatographic Strip Test for Falciparum Malaria

Health Need Addressed

More than two billion people live in malarious regions of the world. As a result, more than 300 million new cases of malaria occur each year, causing several million deaths worldwide.

Microscopy is the standard method for diagnosis in many parts of the developing world, but it requires considerable technical skill to perform well and is time consuming. Currently, there are several rapid malaria tests on the market, but many of these are still cost-prohibitive for use in resource-limited settings. A simple, low-cost test is urgently needed for the rapid and accurate identification of falciparum malaria infection in smaller clinics and hospitals where microscopy cannot be adequately performed.

HealthTech IV Solution and Potential Impact

The falciparum malaria immunochromatographic strip ICS test, developed during HealthTech III, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify *Plasmodium falciparum*-specific, histidine-rich protein 2 (PfHRP-2) antigen in blood. The test can be completed in 20 minutes and may be performed by technicians with minimal training. This simple, rapid technology has enabled testing for falciparum malaria in rural or small clinics or hospitals in the developing world, and accurate results can be returned the same day. The test can also be used by epidemiological surveillance teams in the field to gather baseline data or to assess the effect of public health interventions. The test can supplement or confirm infection in conjunction with microscopic diagnosis of malaria at central reference facilities.

Several rapid falciparum malaria tests are now commercially available, but many of these are still cost-prohibitive for use in developing countries. If the cost of the key antibody reagents in the test could be reduced, this would result in the commercial production of a more affordable diagnostic tool.

Milestones and Accomplishments Achieved in the Past Six Months

- Technical assistance was provided to the Western Pacific Regional Office (WHO, Manila, Philippines) for the development of quality assurance programs for rapid malaria tests.
- The cloned monoclonal antibody supernatants were purified and the three monoclonal antibodies in the ICS test format were screened.
- Preliminary data, using a small number of clinical samples, indicates that the purified monoclonals are sensitive and specific to PfHRP-2. These preliminary results indicate that these newly developed antibodies may become a cost-effective alternative to the currently available antibodies. Further evaluation is needed with a larger number of control samples, and the threshold detection of level of the assay needs to be determined.
- PATH identified and contracted with a research collaborator to expand three monoclonal antibody clones in order to produce sufficient antibody for ongoing test development and validation.

Problems Encountered and Actions Taken

- **Problem:** While the antibodies are sensitive and specific to HRP-II, they do not perform optimally in the current test system when a whole-blood sample is used.

Action: Continue to optimize the assay by experimentation with capture and detection systems.

Status of Project as of September 2003

Significant progress has been made in the evaluation of these new antibody reagents for HRP-II. If the specificity problems observed with whole-blood samples can be overcome, it is anticipated that these reagents will be both sensitive and specific for HRP-II.

Plans for the Next Six Months

- Optimize the chemistry and concentrations of the capture and detection systems.
- Continue laboratory-based evaluations of the three monoclonal antibody reagents in the ICS format.
- Produce test prototypes and forward these prototypes to an independent party willing to retrospectively assess the performance of the test if the laboratory evaluation data are satisfactory.
- Identify a suitable commercial manufacturer for production of the monoclonal antibodies.

Diagnostics for Surveillance

Health Need Addressed

Health information systems (HIS) in developing countries require accurate disease diagnoses in order to track and intervene against outbreaks of easily transmissible, infectious diseases. HIS also need diagnostic data to track diseases that are not highly contagious but are of public health importance. Most HIS rely on the collection of infectious samples from remote health facilities and their transport to central laboratories for diagnosis. Problems with transporting these samples are a major constraint.

HealthTech IV Solution and Potential Impact

The use of rapid diagnostic tests in remote health facilities or the introduction of central laboratory tests that can be done on dried blood spot samples could potentially solve the problem of transporting laboratory samples for health surveillance systems. PATH's experience in the development, adaptation, testing, and introduction of diagnostic tests for resource-poor settings can be used to integrate appropriate diagnostics into HIS. Specifically, PATH is interacting with the USAID-supported Partners for Health Reform Plus (PHR+) project on their activities in assisting several African countries with their HIS to evaluate the integration of rapid diagnostics into their systems.

Milestones and Accomplishments Achieved in the Past Six Months

- Held follow-up discussions with PHR+ regarding Tanzania activities. The lack of support and interest by the government in operations research on diagnostic testing along with a lack of surveillance infrastructure make initiation of HealthTech activities difficult. We continue to monitor the situation via PHR+ staff for any changes in the situation.
- Completed another update of a summary of commercially available rapid diagnostic tests or central laboratory tests that can or might be adapted to work with dried blood spot samples for diseases of interest in Ghana. This summary will provide the basis for discussions with the Ghanaian MOH on possible HealthTech inputs to their health surveillance system.
- Initiated contact with MOH staff in Ghana and organized a visit by PATH to take place in October to discuss possible HealthTech collaboration in developing the health surveillance system there.
- At the suggestion of USAID Washington, initiated contact with Bradford A. Kay, Coordinator of Laboratory Capacity Development at the WHO Department of Communicable Disease Surveillance and Response, to discuss possible collaborations with HealthTech on surveillance diagnostics. We have scheduled a conference call for October.

Problems Encountered and Actions Taken

- **Problem:** The health surveillance systems in both Tanzania and Ghana are in early stages of development. It is difficult to do comparison studies of different diagnostic techniques in systems and situations that are rapidly changing.

Action: HealthTech will work closely with PHR+ and the CDC to choose appropriate sites for our work.

- **Problem:** In Tanzania, and to a lesser extent Ghana, the MOH is resistant to piloting any interventions or programs.

Action: HealthTech is marketing our inputs as operations research and cost-effectiveness studies.

Status of Project as of September 2003

An initial review of opportunities to work in Tanzania has been disappointing, but we continue to monitor the situation. Discussions with the WHO Lyon laboratory and the Ghana MOH are planned for October 2003 to determine opportunities for collaboration there.

Plans for the Next Six Months

- Organize a visit to Ghana to gauge the MOH's interest and possible uses for improved diagnostic testing in their surveillance system.
- Hold discussions with WHO's laboratory staff regarding possible collaborations.
- Develop a work plan for an operations research project in either Tanzania or Ghana, based on the results of the October Ghana meeting.

Rapid Diagnostics Web Site

Health Need Addressed

Program planners, managers, and laboratory staff need clear, well-documented information about choices of available diagnostic tests in order to make informed decisions, particularly when resources are limited. Because rapid diagnostic tests are a relatively new group of technologies, comprehensive information is difficult to find. PATH regularly receives inquiries about the availability and appropriate uses of a wide range of rapid diagnostic tests.

HealthTech IV Solution and Potential Impact

Based on PATH's substantial experience and knowledge about test development and introduction, HealthTech has set up the Rapid Diagnostics web site, which provides summaries of important information as well as links to additional resources. The web site strives to promote the appropriate use of rapid diagnostic tests. Staff developed the site to bring together information on available rapid test technologies for hepatitis B, HIV, malaria, and syphilis, and provide references to peer-reviewed literature detailing the accuracy of these tests and their appropriate use. A comprehensive table for each disease includes manufacturer contact information for available rapid diagnostic tests for four main diseases. Potential impact of this web site includes the ability of planners, managers, and laboratory staff to make better diagnostic test choices and improve program design both for individual diagnosis and disease surveillance.

Milestones and Accomplishments Achieved in the Past Six Months

- Monthly reports demonstrate that the number of visitors to www.rapid-diagnostics.org fluctuates between 10,000 and 12,000 visitors per month.
- The top sections visited each month are the information pages on HIV, accuracy, syphilis, and hepatitis B. Each of these pages receives at minimum 300 visits per month.
- In June 2003, an update to the manufacturer contact page was made and new links to relevant information on HIV, syphilis, malaria, and hepatitis B were added, including diagnosis algorithms, current state of rapid diagnostics, general performance characteristics, statistical analysis, and current initiatives to improve the quality and use of rapid diagnostic tests.

Problems Encountered and Actions Taken

- **Problem:** It is difficult to keep manufacturer information and web site links up to date.
Action: This information is updated twice annually.
- **Problem:** It is a challenge to increase the visibility and linkage of this web site in the context of international public health program managers and medical professionals.
Action: PATH will continue to promote this web site by sending announcements of updates and identifying additional sites with which to link.
- **Problem:** Continued funding for maintenance, promotion, and updating of this site is uncertain beyond 2003.
Action: PATH will look for other sources of funding.

Status of Project as of September 2003

The web site is totally operational and being accessed regularly by people seeking information on rapid diagnostic tests.

Plans for the Next Six Months

- Update references and links regularly, including available references on evaluation of test performance.
- Design a user survey to identify what needs are met and what additional user needs should be included on the web site.
- Continue implementation of introduction activities to promote the web site.
- Respond to inquiries resulting from web site contact link.
- Monitor web site usage; identify geographical and organizational distribution of web site visitors and identify how they use the available diagnostic information.

Basic Delivery Kit

Health Need Addressed

High rates of maternal and perinatal mortality in developing countries indicate a crucial need for new and innovative interventions for pregnancy and neonatal care. Most women have no access to maternity services due to distance, cost, and local customs; many give birth alone. High rates of neonatal and maternal tetanus and sepsis indicate a need for education and materials focused on clean birth practices.

HealthTech IV Solution and Potential Impact

The basic delivery kit is an inexpensive, simple kit designed to help create a clean birthing



environment, particularly for home births.

Based on a needs assessment in rural community settings, the contents selected for inclusion in the kit sold in Nepal include a clean razor blade, clean cord ties, a small bar of soap, a cord-cutting surface, pictorial instructions and a polyethylene delivery sheet. The delivery kit is designed for use by trained and untrained traditional birth attendants, family members, and women who give birth unassisted in the home.

Following a PATH-sponsored delivery kit conference that took place in Nairobi,

Kenya, in March 1999, several African countries requested PATH's technical assistance in their safe motherhood or maternal and child health programs to implement the development, promotion, and use of delivery kits. The potential impact of the development and promotion of kits in local communities in Africa is great. PATH is currently exploring partnership opportunities and evaluating the effectiveness of a single-use kit on preventing cord infection in Africa.

Milestones and Accomplishments Achieved in the Past Six Months

- PATH continues to distribute the *Basic Delivery Kit Guide* to individuals and institutions around the world. Approximately 20 new copies were shipped out in the past six months, for a total of nearly 570 since publication. PATH will be switching to electronic distribution of the guide via our web site beginning in October 2003.
- The article "Acceptability and Use of Clean Home Delivery Kits in Nepal: a Qualitative Study" authored by PATH staff person Siri Wood and independent consultant Monique Beun was accepted for publication by the international *Journal of Health, Population and Nutrition* (JHPN) in August 2003.
- Under a HealthTech subagreement, the MOH and the National Institute of Medical Research (NIMR) are conducting a combined quantitative/qualitative evaluation of the single-use United Nations Population Fund (UNFPA) delivery kit in Mwanza, Tanzania. The purpose of the study is to determine the immediate impact of delivery kits on reducing cord infection. As of September 2003:

- A total of 2,606 women had been enrolled and interviewed so far. The preliminary data compiled in April 2003 are from only 1,614 women, so the total number of study enrollees will need to be determined before the study's power to detect a significant difference (n=5,448 per protocol) can be determined. A descriptive analysis will be provided if the requisite number of women is not obtained.
- Preliminary results are favorable. Regression modeling indicates that having a bath before delivery and use of the kit had a significant impact on puerperal sepsis, and that the probability of developing cord infection is smallest for infants whose mothers had a bath before delivery and who used the kit. Cross tabulations indicated that there is a lower chance of developing a cord infection if a new tie (included in the kit) is used.
- Qualitative research activities were concluded in early 2003 and reported on in the last semi-annual HealthTech report.
- The tenth and final cluster was enrolled in the study on February 3, 2003. The last women enrollees gave birth and were interviewed during June and July 2003.

Problems Encountered and Actions Taken

- **Problem:** As of September 2003, only 2,606 women had been enrolled in the study. The last batches of data are still coming in from the field; however it is likely that the study will not reach the required sample size of 5,448 as projected in the protocol.

Action: The total number of enrollees will be determined by the end of October, when all data is received from the field. PATH and NIMR will perform a descriptive analysis if the number of enrollees does not have enough power to detect differences.

Status of Project as of September 2003

The study team is finalizing data collection and entry, cleaning data, and preparing for analysis. Preliminary analysis performed on partial data in April 2003 (n=1,614) suggests highly favorable results with lower rates of sepsis and cord infection among kit users and their infants.

Plans for the Next Six Months

The study will conclude and the final reports written by January 2004.

Vasectomy by Cautery

Health Need Addressed

According to a study by Family Health International (FHI), the vasectomy technique that is most commonly used in low-resource settings—simple ligation with excision of a short segment of the vas—appears to have a relatively high failure rate, with reported pregnancy rates as high as 4 percent at the end of three years. An improved method incorporating vas occlusion using cautery could provide increased efficacy at costs appropriate for low-resource settings.

HealthTech IV Solution and Potential Impact

Currently, FHI and EngenderHealth (EH) are collaborating on a study to determine the clinical advantages to vasectomy using cautery and safe and dependable procedural methods to use in conjunction with cautery. In addition to this field research, PATH, under HealthTech funding, has been asked to evaluate the physical durability and the potential for reuse of a thermal cautery device along with potential redesign or cost-reduction opportunities. The long-term goal of this collaboration is to introduce a cautery vasectomy technique, in conjunction with recommended procedural and reuse methods, for introduction into low-resource settings.

Milestones and Accomplishments Achieved in the Past Six Months

- Received a bid for manufacturing of cautery handle, tips, and sterile sleeves at a Chinese contract manufacturing facility. At moderate production volumes, the costs were reduced to approximately US\$1 for the handle and US\$0.38 for a cautery tip and sterile sleeve.
- Personnel attended a meeting with FHI and EH in June to discuss the results of a randomized control trial of vasectomy techniques and an observational study of vasectomy using cautery. PATH helped to facilitate a round-table discussion of various cautery methods. PATH also presented results from an initial cautery tip reuse evaluation conducted in September 2002 and the costs of generic device production in China.
- Developed a scope of work for a cleaning evaluation (to be completed at PATH) and a sterilization and disinfection evaluation (to be completed at a contract laboratory.) Currently, the protocols are being reviewed by FHI and EH, and testing should begin in November.

Problems Encountered and Actions Taken

No significant problems have been encountered.

Status of Project as of September 2003

Work in progress to verify cleaning effectiveness and sterilization/disinfection efficacy of the cautery tips to support the evidence for the safety of reuse.

Plans for the Next Six Months

- Coordinate the activities of ongoing cleaning and sterilization evaluations.
- Present data from cleaning, sterilization, and disinfection evaluations in December at the next experts' meeting convened by FHI and EH.

Microbicides Applicator Evaluation

Health Need Addressed

In the midst of the growing AIDS pandemic, the use of microbicides could potentially provide urgently needed options for women and men seeking protection from HIV and other sexually transmitted diseases. With over 60 potential microbicides in clinical and preclinical trials today, researchers are closely examining the safety and efficacy of each potential product. Once a product becomes available to its target audience, however, uptake and the effectiveness of the microbicide will depend on many additional factors including affordability, acceptability, the consistency of use, and optimal application of the microbicide within the vagina. The applicator, as a delivery mechanism for the microbicide, will play a central role in each of these factors, including cost, acceptability, dose delivery, and dose effectiveness.

HealthTech IV Solution and Potential Impact

To assess the benefits and limitations of existing applicators for use with microbicides in low-resource settings, PATH conducted an initial applicator evaluation in 2003. This evaluation included a literature review and interviews with many of the investigators currently leading microbicide clinical and preclinical trials. The results from this study indicated that issues of applicator cost, safety, and reuse were considered critical for the future acceptability and accessibility of microbicide products in low-resource settings, yet had not been thoroughly investigated in prior research.

PATH is now conducting three studies to address the issues of cost, safety, and reuse that were raised in the desk study. Data collection from each of these studies will be completed by December 2003, and results and recommendations will be compiled by March 2004. If results of the safety study, acceptability study, and material analysis indicate a need for further refinement or adaptation of applicators for resource-poor settings, PATH would establish collaborations with industry and private-sector partners as needed to adapt existing applicator designs

Milestones and Accomplishments Achieved in the Past Six Months

Microbicide Applicator Acceptability Study

- PATH, established a collaboration with Profamilia in the Dominican Republic and the Reproductive Health Research Unit in Durban, South Africa, to conduct a study to characterize and prioritize women's needs as they relate to vaginal applicator features.
- Developed protocol and survey instrument and obtained approval by PATH Human Subjects Protection Committee (HSPC) and by local ethical review committee in field sites as required.
- Conducted researcher training and pretest of survey instrument in both field sites. Data collection is underway in both field sites.

Microbicide Applicator Safety Study

- In collaboration with Profamilia in the Dominican Republic, PATH is conducting a clinical safety study among 20 women to assess and compare the effect of three applicators on symptoms and signs of vaginal irritation as seen by colposcopy.
- Developed protocol in collaboration with Profamilia and obtained approval by PATH HSPC and ethical review committee at Profamilia.

- Determined final selection of study applicators through discussions with collaborators, CONRAD, manufacturers, and researchers. Applicators procured and provided to study site.
- Initiated study: 11 volunteers enrolled, 5 completed study to date. Clinical monitor contracted and completed first of two monitoring visits.

Material and Design Feasibility Analysis

- In addition to these field evaluations, PATH is conducting several mechanical tests of different applicator designs and materials to characterize their features as they pertain to cost, reuse, and disposal.
- Tests include cleaning effectiveness of a reusable applicator, applicator function after high temperature exposure, and product loss from evaporation. Additional desk research will be conducted to determine the degradability of standard plastics used in high volume/low cost injection molding (e.g. polyolefins), degradability of cardboard materials used in single-use applicators, and products of combustion of standard plastics and cardboard.
- Sourced quotes for external contracting of cleaning effectiveness testing.
- Developed desk research objectives to determine (1) degradability of standard plastics used in high volume/low cost injection molding (e.g. polyolefins), (2) degradability of cardboard materials used in single-use applicators, (3) products of combustion of standard plastics and cardboard.

Problems Encountered and Actions Taken

- **Problem:** We originally intended to use placebo-filled applicators for use in the safety study. In discussions with clinical trial researchers about the development of a new “universal placebo,” we learned that the new placebo would not be available in the time frame necessary for our study. Also due to this shift in placebo product being used in clinical trials, study managers were not able to ensure us a source of applicators with preexisting placebo formulas. Additionally, through discussions with colposcopy experts at CONRAD and Profamilia, the determination was made that a placebo or gel released by the applicator during use would actually confound colposcopy results, given our desired objective was to measure the effect of the applicator alone.

Action: To address these problems, we developed the safety study protocol to include the use of empty applicators without use of placebos, and sourced applicators directly from the manufacturers. This final protocol was reviewed and found acceptable by colposcopy experts at CONRAD, Profamilia, and PATH.

Status of Project as of September 2003

Clinical safety study, acceptability study, and material and design feasibility study are all in progress. Data collection is to be completed in December 2003 and results available in March 2004.

Plans for the Next Six Months

Microbicide Applicator Acceptability Study

- Complete data collection in South Africa and Dominican Republic.
- Analyze data with conjoint analysis consultants and write up results of study.

Microbicide Applicator Safety Study

- Complete data collection in Dominican Republic.
- Clinical monitor to conduct close-out monitoring visit at site.
- Analyze data with Profamilia investigators and write up results of study.

Material and Design Feasibility Analysis

- Contract with external agency to conduct cleaning tests and provide report to PATH.
- Complete mechanical testing and desk research.
- Analyze data and write up results of studies.
- Submit abstracts for the acceptability, safety, and material and design studies, as well as the desk study (4 total) to the Microbicides 2004 Conference. If accepted, presentations on study findings will be made in March 2004 at the Microbicides Conference.

Development of a Vaccine Against Human Schistosomiasis

Health Need Addressed

Schistosomiasis affects approximately 200 million people worldwide, over 85 percent of whom are in Africa. Two species infect people in Africa, *Schistosoma haematobium* and *S. mansoni*. The former is relatively easy to diagnose because of the classical symptom of blood in the urine and is easy to treat with a single oral dose of praziquantel, a generic drug costing less than 25 cents per treatment. *S. mansoni*, while equally easy to treat, is very difficult and expensive to diagnose, compared to the cost of treatment. There is no specific symptom when infected; yet the long-term consequences are devastating. A vaccine capable of protecting children from infection would be a very useful tool for the control of this disease. Proof of principle had been established by irradiating larval worms and protecting laboratory animals against *S. mansoni* and cows against *S. bovis*. In 1995 six candidate vaccines were identified by a WHO committee, which investigated the status of vaccine development. Two of these candidates were selected for development including Phase One human trials supported by USAID/Cairo, under the Schistosomiasis Vaccine Development Project (SVDP).

HealthTech IV Solution and Potential Impact

SVDP was a complex project involving eight partners, of which three participating partners were situated in Egypt—the Egyptian Reference Diagnostic Center (ERDC), the High Institute for Public Health, Alexandria (HIPH), and the U.S. Navy Medical Research Unit, Cairo (NAMRU-3). There were two U.S. Government partners, CDC (Atlanta) and National Institute of Allergy and Infectious Diseases (NIAID, Bethesda). There were three other partners involved, PATH in Seattle; Harvard School of Public Health (HSPH) in Boston; and Bachem, a commercial immunology company based in California. With funding provided from the USAID mission in Egypt, PATH was responsible for project and administrative management, procurement, training and travel arrangements, intellectual property rights issues, and subcontracting the services required from both the HSPH and Bachem.

Milestones and Accomplishments Achieved in the Past Six Months

- At the request of the USAID Mission/Cairo, PATH procured and shipped a final order of supplies and small equipment to the ERDC laboratory for their use in completing the project.
- Dr. Maged Al Sherbiny of ERDC and Dr. Sameh Al Gayyar of the USAID Mission/Cairo visited USAID Washington to discuss future assistance to the ERDC. Any further assistance from PATH would be provided under a future project, yet to be defined.

Problems Encountered and Actions Taken

No problems were encountered during this time period.

Status of Project as of September 2003

The SVDP project was completed on September 30, 2003.