HealthTech IV

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Table of Contents

Executive Summary 1

Vaccine Vial Monitors 2

Cold Chain Technologies 5

Uniject for Infant Immunizations 7

Introduction of Injectable Contraceptives in the Uniject Device 9

Gentamicin in Uniject Devices 11

Mass Campaign Jet Injector 13

Safe Medical Waste 15

Retinol Binding Protein Enzyme Immunoassay (RBP-EIA) 17

Immunochromatographic Strip Test for Tuberculosis 20

Immunochromatographic Strip Test for Gonorrhea 22

Immunochromatographic Strip Test for Chlamydia 24

Immunochromatographic Strip Test for Falciparum Malaria 25

Diagnostics for Surveillance 26

Rapid Diagnostics Web Site 28

Vasectomy by Cautery 29

Basic Delivery Kit 30

Development of a Vaccine Against Human Schistosomiasis 32

Executive Summary

The HealthTech IV program began officially on October 1, 2001, but continued the many years of work at PATH developing, adapting, testing and advancing health, family planning and nutrition technologies under HealthTech I, II, and III. This report summarizes the progress made during the second six months of HealthTech IV from April 2002 through September 2002, and includes milestones and objectives achieved over the last six months, problems encountered, and plans for the next six months.

The following are significant achievements over the last six months:

- Assisted with further advancement of vaccine vial monitors (VVMs). Nine of the 22 UN (United Nations)-prequalified suppliers of Expanded Programme on Immunization (EPI) vaccines other than oral polio vaccine (OPV) have included VVMs on their products. VVMs are therefore now available on all OPV and a portion of BCG, yellow fever, measles, MR, MMR, hepatitis B, and tetanus-toxoid vaccines supplied through UNICEF.
- Completed evaluation of the Indonesia vaccine cold chain and documented high rates of vaccine freezing. Demonstrated the feasibility of several options for eliminating or modifying the cold chain to reduce freezing without causing excessive heat exposure. Submitted manuscript for publication in the *Bulletin of the World Health Organization*.
- Submitted manuscript for publication in the *Bulletin of the World Health Organization* which describes the advantages and disadvantages of monodose vaccines and self-contained unit-dose vaccine administration systems (such as the Uniject™* prefill injection device) compared to multi-dose presentations.
- Completed immunization cost-effectiveness model comparing the costs of injection safety strategies. The model is available for specific applications.
- Conducted design stage field evaluation of the Felton mass campaign jet injector prototypes in Senegal (three field site locations) in September 2002. The device was well received by local health workers.
- Conducted an evaluation of needle removal devices as part of a regional immunization waste management workshop in Senegal, in cooperation with the Senegal Ministry of Health and the Children's Vaccine Program at PATH (CVP). Included two PATH needle remover designs as well as two other manufacturers' devices. Results showed high acceptance of the needle removal concept, and the workshop resulted in the decision to procure 1,000 devices for use in Senegal and Ivory Coast.
- Received feed back from external reviewers on "RBP-EIA: A New Approach to Assessing Vitamin A Deficiency", a resource that describes the test and its proposed use and value. The reviewers found the RBP-EIA to be a practical surrogate for serum retinol and provided suggestions for future field validation studies.
- Launched the rapid diagnostics web site (www.rapid-diagnostics.org) that includes information on malaria rapid tests and a list of commercial manufacturers and distributors.
- Continued the prospective field evaluation of the gonorrhea (GC) immunochromatographic (IC) strip test in Johannesburg, South Africa, which is progressing well. Enrollment of male subjects has been completed and data analysis is underway. Fifty percent of the female subjects have been enrolled and it is anticipated that final enrollment would be completed by the end of December.
- Participated in meetings in Washington, D.C., with USAID, Partners for Health Reform Plus (PHR+), Centers for Disease Control (CDC), and Tanzanian health officials on development of a Health Information System in Tanzania, that may include rapid diagnostics for infectious diseases.

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* Uniject™ is a trademark of BD.

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 the 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. This often results 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 using the most heat labile of all currently used vaccines. VVMs are also 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 (such as DPT, TT, Td, DT, Hib, and hepatitis B). Once VVMs are on all vaccines, the level of vaccine wastage indicated by the VVMs 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. In this way, the cold chain may be "tuned" to eliminate costly redundancies inherent in the system today.

Milestones and Objectives Achieved in the Past Six Months

Ensuring Access—Removing Impediments to Vaccine Vial Monitor Implementation

- As of September 2002, all 4 suppliers of OPV to the UN continue to include VVMs on their products. Nine of the 22 UN-prequalified suppliers of EPI vaccines other than OPV have included VVMs on their products. VVMs are therefore available on all OPV and a portion of BCG, yellow fever, measles, MR, MMR, hepatitis B, and tetanus-toxoid vaccines supplied through UNICEF.
- Annual demand for VVMs for 2001 was 160 million units. From January to September 2002, approximately 122 million units were sold to vaccine producers.
- The Global Alliance for Vaccines and Immunization (GAVI) Research and Development (R&D) Task Force continues to place a high priority on VVM implementation to help ensure quality of vaccines and to provide new mechanisms for storage and transport to help prevent damage to freeze-sensitive vaccines.

Informed Selection—Technical Assistance to Immunization Programs

- A recent cold chain study of hepatitis B vaccine in Uniject in Indonesia utilized VVMs and resulted in some useful findings that will be extracted for future flexible cold chain studies with regard to exterior VVM placement on boxes of vaccine, exposure to sunlight, and training material content.

- HealthTech has provided technical assistance to Beijing Tiantan Biologicals (China) and the Ministry of Health with specification and donation (from LifeLines) of VVMs in preparation for an upcoming hepatitis B vaccine study.

Ensuring Appropriate Use of Vaccine Vial Monitors

- HealthTech staff provided further review to the WHO document entitled "Getting Started with VVMs" following field testing of the document in Vietnam.
- HealthTech staff also reviewed and edited the WHO documents entitled "Temperature Indicators for Vaccines and the Cold Chain" and "Factors Affecting Vaccine Wastage and Monitoring Vaccine Wastage as a Programme Quality Indicator." Both documents incorporate information about VVMs in anticipation of broad availability of VVMs.

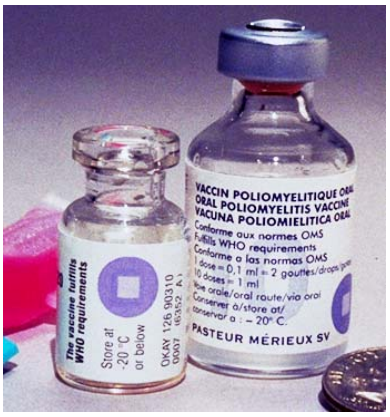
Other

- Dr. Christopher Elias, President of PATH, gave a presentation on VVMs at a joint board meeting of the Rockefeller Foundation and California Endowment entitled "Health, Technology, and Philanthropy" in June 2002.

Problems Encountered and Actions Taken

Problems

- The following UNICEF vaccine suppliers are not moving forward with VVM implementation for vaccines other than polio or have announced delays in excess of one year: Aventis Pasteur (Canada and France), Cheil Jedang (Korea), CSL (Australia), Evans Vaccine (UK), Glaxo SmithKline (Belgium), Human Co. (Hungary), Merck Vaccine (USA), Statens Seruminstitut (Denmark), Serum Institute of India (India), and Wyeth Pharmaceuticals (USA). Of this group, Serum Institute of India, Aventis Pasteur, and Glaxo SmithKline are the largest and most influential suppliers. Glaxo SmithKline has announced its intent to implement VVMS by the end of 2003.



- UNICEF is reluctant to promote, identify, and adopt positive incentive mechanisms for vaccine manufacturers to supply products with VVMs. A method of encouraging a few key suppliers who are, as yet, unwilling to move forward is needed. UNICEF must agree upon such a method with other GAVI partners.
- UNICEF will not or cannot use a distribution policy that takes VVMs into account. Therefore, countries do not know whether or not any given shipment will receive VVMs and cannot plan for their use. Partial VVM availability is therefore almost worthless unless this issue can be resolved.

Actions

- At this stage, most problems are due to issues between UNICEF Supply and other GAVI partners. HealthTech will continue to provide technical support, as needed.
- Training must be conducted on a global basis and immunization programs must be prepared to use VVMs on vaccines when they arrive, since targeted training is impossible. PATH will continue to support WHO with finalizing training materials and will opportunistically provide technical assistance to countries through the CVP, HealthTech, and GAVI activities.

Plans for the Next Six Months

- Monitor progress with compliance to VVM specifications as well as inclusion of VVMs in future specifications and provide data and assistance to partners, as needed. The availability of VVMs hinges on the ability of UNICEF and other GAVI partners to work collaboratively, share essential information, and give unified messages to vaccine producers. Until these issues are resolved, availability of VVMs on all EPI vaccines is unlikely to occur at a level that will make a significant difference to countries because they will receive only sporadic shipments of product with VVMs with no prior notification. These problems must be taken to the highest levels of the UN organizations to ensure resolution. They will be discussed at the GAVI Partners Meeting in Dakar, Senegal, in November 2002.
- Continue to monitor and assist with publication of VVM training materials at WHO and the integration of VVMs into other relevant immunization training materials and documents.
- Opportunistically provide technical assistance to countries through CVP, HealthTech, and GAVI activities.

Cold Chain Technologies

Health Need Addressed

The cold chain is the "vehicle" for getting vaccines to their intended targets while guarding their efficacy. A limited cold chain reduces the reach of vaccines into peripheral areas, denying infants in these areas access to lifesaving vaccines. Even worse, a cold chain that inactivates vaccines by freezing them or allowing over-exposure to heat can result in infants receiving ineffective vaccines with the epidemiological consequences of unvaccinated populations within areas of assumed vaccine coverage.

HealthTech IV Solution and Potential Impact

The conventional cold chain is unreliable, inefficient, and in many cases, harmful. The introduction of VVMs, new vaccines, and new refrigeration technologies, and increased awareness of freeze damage risks, present significant opportunities for creating new approaches to vaccine storage and distribution. The key priorities for streamlining vaccine distribution are:

- Avoid vaccine freezing.
- Create capacity for future vaccines and monodose presentations.
- Increase system reliability, performance, and affordability.

Under HealthTech, and in collaboration with other agencies and experts, PATH is exploring solutions that satisfy each of these priorities. Because of the broad variation in country conditions and opportunities, a multi-faceted approach is likely to yield the best results. Proposed solutions fall in several categories, including raising awareness of the current problems and potential solutions, technology development, and modeling of new systems.

Milestones and Objectives Achieved in the Past Six Months

- Completed Indonesia cold chain evaluation. Documented high rates of vaccine freezing. Demonstrated the feasibility of several options for eliminating or modifying the cold chain to reduce freezing without causing excessive heat exposure. Submitted manuscript for publication in the *Bulletin of the World Health Organization*.
- Led international technical team to visit Indonesia to resolve cold chain problems. Developed action plan.
- Began testing of VaxiCool ice-free refrigeration and outreach system in the shop facilities in Seattle.
- Began experimentation and design to try to eliminate vaccine freezing in existing cold boxes.
- Participated in GAVI R&D technology task force to advance the cold chain agenda.

VaxiCool ice-free refrigeration system

Problems Encountered and Actions Taken

- **Problem:** Energy Storage Technologies, Inc. (EST) of Dayton, Ohio, USA, supplier of target technology—VaxiCool™* ice-free solar refrigeration system—was unable to provide a system for testing in a timely manner. This delayed plans for evaluation and field assessment.

  Action: To ensure their commitment to this project, PATH continues to work closely with EST in refining technology, assessing the market, and gathering evidence of need.

- **Problem:** During meetings with the Indonesia Ministry of Health regarding the cold chain, PATH advocated a proactive approach to developing an action plan and resolving the problems.

  Action: PATH is leading the effort to update options and finalize an action plan.

Plans for the Next Six Months

- Continue to work with EST, to adapt and field test the VaxiCool system which is currently supplied for military vaccine applications. PATH proposes to evaluate the complete ice-free outreach system in two developing countries in 2003.
- Develop and test "freeze-proof" and "cool chain" technologies such as eutectic cold packs and new vaccine carrier designs.
- Document the thermostability of freeze-sensitive vaccines and sponsor laboratory testing as necessary.
- Publish results of the study of the Indonesia cold chain and work to expand this model in Indonesia and beyond.
- Explore with WHO ways to accelerate the introduction of VVMs on all vaccines. The eventual availability of VVMs on all UNICEF-supplied vaccines can facilitate the ability of countries to remove heat-stable vaccines from the cold chain.
- Work with WHO on a policy document on the "flexible cold chain" to assist countries with implementation.
- Continue searching for appropriate freeze indicator technology and applications.

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

Uniject for Infant Immunizations

Health Need Addressed

Recent surveys in developing countries have revealed that 30 to 50 percent of injections are not sterile. Disposable syringes are frequently reused, and reusable syringes are often improperly sterilized. The risks of transmission of bloodborne pathogens such as hepatitis B and human immunodeficiency virus (HIV) are great. New methods are required to ensure that a sterile syringe is available for each injectable dose delivered.

HealthTech IV Solution and Potential Impact

The Uniject prefill injection device was developed and advanced during HealthTech I, II, and III and has been licensed to BD for commercial production. It is a prefilled, single-dose injection system for use with vaccines and other medicaments, and is specifically designed to prevent reuse. Uniject devices are available in 0.5- and 1.0-ml dose sizes with any standard-size needle.

Recent improvements in vaccine stability have resulted in initiatives to relax the rules for cold storage of some vaccines (e.g., tetanus toxoid and hepatitis B vaccine) thereby facilitating their delivery to hard-to-reach areas. The Uniject device is an ideal delivery mechanism for these vaccines. This technology simplifies the act of giving an injection, makes the unsafe reuse of the syringe impossible, and reduces the burden on logistics systems by making premeasured medicament, needle, and syringe available at the same place and time. Uniject devices may be appropriate for use in the home or community by outreach workers who do not traditionally deliver injections.

Indonesian child being given a dose of hepatitis B vaccine in a Uniject device

Milestones and Objectives Achieved in the Past Six Months

- Submitted manuscript for publication in the *Bulletin of the World Health Organization* which describes the advantages and disadvantages of monodose vaccines and self-contained unit-dose vaccine administration systems (such as the Uniject device) compared to multidose presentations
- Completed immunization cost-effectiveness model comparing the costs of injection safety strategies. The model is available for specific applications.
- Completed cost-effectiveness analysis of the hepatitis B (HB)-Uniject device in Indonesia (CVP co-funded).
- Conducted field visit to evaluate HB-Uniject device introduction in Indonesia (CVP co-funded).
- Prepared CVP report on HB-Uniject device introduction in Indonesia (CVP funded).
- Prepared TT-Uniject device introduction in Uganda (UNICEF co-funded).
- Using PATH introduction materials, UNICEF introduced TT-Uniject in Mali. Introduction was highly successful and widely publicized by UNICEF.
- Developed Uniject-sized outreach disposal box (capacity 75 Uniject devices).
- Clarified controversial issues surrounding reportedly high wastage rates for Uniject production and pricing.

Problems Encountered and Actions Taken

- **Problem:** Delay in approval by WHO of HB vaccine (manufactured by BioFarma and packaged in the Uniject device in Indonesia) has delayed field introduction in GAVI programs. This in turn has delayed the accumulation of additional experience with the HB-Uniject device that is needed to build the interest of large vaccine manufacturers and field programs.

  Action: PATH continues to provide technical assistance to BioFarma and monitor the WHO approval process.

- **Problem:** UNICEF temporarily rescinded BioFarma's certification to provide vaccines to UNICEF. This derailed PATH's plans to evaluate TT-Uniject devices in Uganda under a UNICEF-funded project.

  Action: PATH is currently looking for a new introduction site.

Plans for the Next Six Months

- Conduct evaluation of TT-Uniject in one or two African countries (with UNICEF funding).
- Introduce HB-Uniject in GAVI programs such as Vietnam (assuming WHO approval in the next two months).
- Prepare results of Indonesia and HB-Uniject evaluation and cost-effectiveness study for publication.
- Continue designing a Uniject-specific outreach disposal box that will include a "how-to" packet to enable countries to manufacture them on their own.

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 7 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 blood-borne 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. Autodisable (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.

Milestones and Objectives Achieved in the Past Six Months

- Pharmacia reported in July that Uniject devices for Depo-Provera and Lunelle have now obtained formal internal "Development Project" status.
  - The project will have a full, new project team from the development group.
  - The project will still have further go/no-go decision hurdles to cross before a product is actively pursued.
- Pharmacia licensing staff contacted BD in July to initiate further discussion/negotiations about exclusivity for this application of the Uniject device.
- Pharmacia, PATH, and BD staff met in August for more detailed discussions of Pharmacia's desire for Uniject exclusivity. Pharmacia clarified their position as one under which they will not register and sell their injectable contraceptives in the Uniject device in any country in which any other company sells any injectable contraceptive in the Uniject device.
- PATH, the USAID Office of Population, and the Concept Foundation met in September to review the broad implications of Pharmacia's position and formulate a consensus strategy. Key elements of that strategy include:

* Cyclofem® is a registered trademark of the Concept Foundation.

- Keeping tone and pace of discussions with Pharmacia positive but measured until after the Pfizer take-over of Pharmacia and the impact on Pharmacia's women's health portfolio and injectable contraceptive product line becomes clearer.
- Coordinating and cross-checking among USAID, PATH, and the Concept Foundation on all discussions held with Pharmacia regarding injectable contraceptives and the Uniject device.
- Consensus view that any commitment to provide Pharmacia with elements of exclusivity for public-sector developing-country markets would include specific performance requirements by Pharmacia.

Problems Encountered and Actions Taken

- **Problem:** Pharmacia's stated demand for global exclusivity for use of Uniject devices for all injectable contraceptives.
  - BD is wary of providing exclusivity without a compensating commitment by Pharmacia for very high, guaranteed purchase quantities—bottom line is that this will be a challenging negotiation between two large, powerful companies.
  - PATH is concerned about both the practical and perceptual implications of Pharmacia having some form of exclusive use of Uniject devices.

  Action: PATH participated in August discussions with Pharmacia and BD to articulate PATH's view and better understand Pharmacia's position.
  - PATH organized a September meeting with the USAID Office of Population and the Concept Foundation.
- **Problem:** Difficult to assess the impact of the recently announced acquisition of Pharmacia by Pfizer, but this could add new complexity. Recent product recall of Lunelle in the United States by Pharmacia may also complicate and/or delay internal Pharmacia/Pfizer decision making regarding the Uniject project.

  Action: PATH is staying in contact with both Pharmacia and others who have insights into Pharmacia's activities—the Concept Foundation and BD.
- **Problem:** On a separate but related track, Applicaciones Farmaceuticas (AF) of Mexico has again further delayed/deferred commercial launch of Cyclofem in Uniject devices in Mexico.

  Action: PATH was asked by AF to join a meeting to review their stated problems with Uniject implementation and develop a project to address these problems.

Plans for the Next Six Months

- As one follow-up to the September meeting of USAID, PATH, and the Concept Foundation, PATH is preparing an update on the current situation with global injectable contraceptive suppliers, with particular emphasis on products and producers potentially relevant to the Uniject device.
- PATH plans to meet with AF of Mexico, as well as BD staff, to better understand the reasons for continued delay in AF launch of Cyclofem in the Uniject device.

Gentamicin in Uniject Devices

Health Need Addressed

WHO estimates that at least 4 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

Uniject injection devices pre-filled 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, to improve neonatal survival from infectious diseases. Community-based health workers could be trained to use gentamicin-Uniject 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 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 gentamicin-Uniject is used safely, properly, and efficiently for infants with severe bacterial infections, then Uniject devices may make a significant contribution to reducing neonatal mortality in developing countries. HealthTech is considering supporting further development of this application of the Uniject device, but meanwhile the following activities have been undertaken under the HealthTech co-funding.

Milestones and Objectives Achieved in the Past Six Months

- Began compatibility and stability testing of a pediatric formulation of gentamicin solution in Uniject prefill injection devices, conducted by Centro AF de Estudios Technologicas S.A. (CAFET) in Mexico.
- Undertook pharmacokinetics analysis to determine appropriate dosages of gentamicin in Uniject devices.
- Drafted and submitted protocol for dosing verification study entitled "Determination of Once-Daily Gentamicin Dosing in Neonatal Patients for Use in Uniject Pre-filled Syringe in Vellore, India" to various ethical review committees.
- Drafted and submitted protocol for dosing verification study entitled "Determination of Once-Daily Gentamicin Dosing in Neonatal Patients for Use in Uniject Pre-filled Syringe in Dhaka, Bangladesh" to various ethical review committees.
- Established collaboration with Save the Children to evaluate the device in an existing field study on gentamicin for newborns.
- Drafted research protocol for Phase II field trial in Bangladesh in collaboration with Save the Children, Johns Hopkins University (JHU), and the Center for Health and Population Research (CHPR) in

Bangladesh. The design reflects evaluation of use of gentamicin-Uniject in the home and at the community clinic by health workers, and at the referral hospital by nurses. Full funding proposal for Phase II field trial in Bangladesh approved by Save the Children Saving Newborn Lives Initiative (SNL), contingent upon a favorable outcome of the dose verification studies.

Problems Encountered and Actions Taken

- **Problem:** Initial results of the compatibility testing indicate the need to reformulate the gentamicin with a buffering agent in order to avoid a decrease in PH levels, or a need to flush with nitrogen versus oxygen (to reduce oxygenation). If the new formulas are acceptable, then compatibility testing can begin. This will take up to six months and will delay the start of field evaluations, so that deadlines for the current collaboration with SNL will likely be missed.

  Action: If the new formulas do not work, the technical feasibility of this use of the Uniject device is questionable and will need to be reconsidered. Otherwise, stability testing will proceed.

- **Problem:** Another challenge is to assess sentiment in the public-health leadership arena around the viability of this product. WHO is convening an expert meeting soon to discuss neonatal antibiotic treatment protocols. It looks as though the standard of care will remain ampicillin/gentamicin (two injections), but there may be an opening for alternative regimens (one injection in Uniject combined with an oral administration) in cases where the standard of care cannot be practiced.

  Action: PATH will need to assess whether the market for this application of Uniject is then big enough to warrant the investment in developing and testing the product.

- **Problem:** Co-funding from USAID for the field trial in collaboration with SNL is still pending.

  Action: PATH will provide timely information to USAID for them to make decisions about supporting this project under HealthTech. Alternative funding sources will also be explored.

Plans for the Next Six Months

- Begin compatibility and stability testing of a pediatric formulation of gentamicin solution in Uniject prefill injection devices shortly after determination of whether or not new formulations are acceptable.
- Conduct Pharmacokinetics analysis to determine the final dosage of gentamicin for compatibility and stability testing. The dose verification study protocols will be implemented at two sites once JHU approval and local ethical review board approval from Dhaka site is obtained.
- Implement the collaboration with Save the Children to evaluate the device in an existing field study on gentamicin for newborns. The study will be nested within a larger neonatal health demonstration project in Sylhet, with the gentamicin Uniject intervention beginning about six months into the larger study, possibly late 2003. This is assuming that the product is ready to go at that time. If not, alternative sites are available in India or Pakistan.

Mass Campaign Jet Injector (formerly called "needle-free injection system)

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, needlestick injuries among health workers, and threats to the community from improperly disposed of and contaminated sharps and needles present serious health risks. Multidose 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, and MedEquipment (earlier called Chemiautomatics Design Bureau—CADB), of Voronezh, Russia, in evaluation, testing, and design refinement of a multidose jet injector that has been developed and manufactured by MedEquipment. This is a high-workload injector, (called the BI-100) intended for use in mass immunization campaigns. The design of the injector involves a novel and effective approach (a disposable protector cap 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 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 Objectives Achieved in the Past Six Months

- Completed design, assembly, and troubleshooting of BI-100 prototypes of the jet injector for use in a design stage field evaluation in Senegal.
- Identified and implemented design changes to protector cap—parts molded and assembled for use in Senegal evaluation.
- Conducted design stage field evaluation of BI-100 prototypes in Senegal (three field site locations) in September 2002. The device was well received by local health workers.
- Conducted design reviews per United States Food and Drug Administration regulatory requirements in support of Felton (identification of necessary design improvements based upon Senegal experience).
- Drafted target design specifications for human serum albumin (HSA) ELISA methodology for human safety testing of the device.
- Continued modification of a manuscript of a risk assessment model comparing needlestick injuries caused by standard or AD needles and syringes versus those caused by jet injectors in mass campaigns with respect to disease transmission.
- Identified collaborator and funding to develop cost model demonstrating the cost-effectiveness and impact of the jet injector in mass immunization campaigns.

Problems Encountered and Actions Taken

International Health Community Acceptance of the Methodology for Human Safety Testing

- **Problem:** Getting final acceptance from the international health community on the methodology for Human Safety Testing of all jet injectors is a challenge. The WHO advisory group on human safety testing met in September 2002 to discuss human safety testing (appropriate biological marker, assay, protocol, etc.) of jet injectors. The Felton injector would be subjected to this testing. Although a firm course of action was not agreed upon by meeting participants, a general consensus was reached for how best to move forward.

  Action: PATH is actively working with members of the WHO advisory group to finalize assay design specifications and is planning for a validation study to support the final assay methodology. The ultimate goal would be a modified or reversed WHO policy regarding the use of jet injectors in mass immunization campaigns based upon favorable results of a safety study.

Felton International Business Status

- **Problem:** Felton has continued to face challenges when attempting to obtain investment for the development of a human injector for mass immunizations in the developing world. Although a certain amount of investment was recently received, more funds are needed to ensure project success. Additionally, the sales of Felton's primary product—animal injector product—are below expectations; Felton had relied on this source of revenue to fund development of the human injector. The promise of collaboration with BD has not materialized, and BD is currently waiting to determine if WHO policy regarding the use of jet injectors in mass immunization campaigns will change based upon favorable results from human safety testing.

  Action: PATH will continue to assist Felton with the identification of potential sources of funding and discussions with potential business collaborators.

Plans for the Next Six Months

The Mass Campaign Jet Injector team at PATH will continue to work with Felton to finalize designs and conduct user evaluations. PATH plans to be primarily involved with final redesign, verification testing, human safety testing, and introduction activities for the BI-100 in 2003.

- Work with Felton to complete the redesign of the injector and protector cap.
- Assist in verification testing per product requirement specifications of final designs (protector cap and injector).
- Collaborate on overall project plan management with Felton.
- Present risk model at the upcoming Needle Free Injection Systems Conference (December 2002).
- Complete cost model comparison demonstrating benefit of jet injector, collaborating with Instituto Nacional de Salud Pública (INSP) in Mexico and CDC.
- Work with WHO advisory group on human safety testing of injector.
- Coordinate with policy makers in international public health community to promote acceptance of BI-100.

Safe Medical Waste

Health Need Addressed

Each year, more than 12 billion injections are administered worldwide. Estimates indicate that more than 50 percent of developing-country injections are unsafe (WHO Injection Safety, Quality of Immunization Services [QIS], August 28, 1998). Safe injection is a high priority for WHO, but the global target set by WHO and UNICEF to provide greater than 95 percent safe injections by the year 2000 is far behind schedule. Safe needle and syringe disposal is an important element of these injection safety goals.

WHO is encouraging use of AD syringes as a tool against syringe reuse. Ironically, the increased use of AD syringes has begun to result in an increase of contaminated needles and syringes that require disposal. Healthcare workers who handle an increasing volume of contaminated syringes and needles are at risk of needlestick injury, which can result in transmission of numerous bloodborne diseases such as hepatitis B, hepatitis C, and HIV. Improper disposal of such syringe waste also 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 that requires minimal handling of the contaminated needles by health care workers and waste disposal personnel. Point-of-use needle removal, or "defanging," provides immediate isolation of contaminated sharps; decreases the required volume of disposal boxes by 20 to 60 percent; and aids in discouraging reuse of potentially contaminated syringes. Integrating such a point-of-use, needle-removal device into a larger disposal system that also includes the disinfection and disabling of used syringes is needed in order to meet the goal of 95 percent safe injections.

Any situation in which a needle and syringe are used is an appropriate setting for point-of-use needle removal and containment. This technology would improve safety for large-scale immunization campaigns, static injection campaigns, and smaller outreach clinics. A technology designed to disinfect and disable used syringes could then be integrated either as part of a modular technology to be used in tandem with a needle-removal device or as a stand-alone processor to prepare bulk sharps waste for ultimate disposal. Specific applications would need to be tailored for each setting.

Milestones and Objectives Achieved in the Past Six Months

- Continued to oversee the transfer of the needle puller technology to PATH's manufacturing partner in India. Evaluated second and third generations of evolving and improving prototypes.
- Contracted for the design of a portable needle cutter with a U.S. firm. Coordinated the development of seven functional prototypes within two months.
- Collaborated with a needle-cutter manufacturer in the United Kingdom, which resulted in a decrease in their pricing by more than 85 percent (to £23 for bulk orders), thereby increasing affordability for developing country programs.
- Conducted a needle-removal device evaluation as part of a regional immunization waste management workshop in Saint Louis, Senegal, in cooperation with Senegal Ministry of Health and the Children's Vaccine Program. Included two PATH needle remover designs as well as two other manufacturers' devices. Results showed high acceptance of the needle removal concept, and the workshop resulted in the decision to procure 1,000 devices for use in Senegal and Ivory Coast.
- Commissioned and completed a splatter and surface contamination test of five needle-removal devices, including the PATH Needle Puller. No device use resulted in contamination. The report summary was posted on the TECHnet web site, and will be presented at Safe Injection Global Network (SIGN) annual meeting.

- Conducted bench evaluations of 4 different needle-removal devices in various stages of development and marketing from external designers and manufacturers.
- Linked the needle cutter manufacturer in the United Kingdom with syringe manufacturers for future supply bundling.

Problems Encountered and Actions Taken

- **Problem:** Interest in the needle puller concept led to a program demand that exceeds current supply.

  Action: The negotiation with the U.K. manufacturer to reduce the price of their device will significantly improve supply in the near future. In the long-term, the Indian manufacturer is expected to provide appropriate devices and the new portable cutter to be scaled up for production.

Plans for the Next Six Months

- Facilitate the manufacture of 1,000 devices by the Indian manufacturer for a WHO field study in India.
- Complete licensing agreement with Indian manufacturer for commercial production.
- Request scale-up plan for new portable needle cutter to incorporate feedback from Senegal workshop in a next-generation prototype.
- Conduct evaluation in India of two needle-remover devices to assess performance during routine use—including durability, ease of needle disposal, cleaning, and reliability.
- Develop needle removal performance specifications for public-sector procurement agencies.
- Collaborate with programs as needed for additional field study opportunities, including a possible upcoming study in Indonesia in the first quarter 2003.

Image of a participant testing one prototype of the needle-puller during an informal user-evaluation

- Continue to network with existing manufacturers and immunization program managers to connect programs with appropriate needle-removal devices.
- Examine other program needs related to syringe and needle waste management such as syringe processing and alternatives to incineration, including conducting a hands-on session at the 2002 annual SIGN meeting.

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 the consequences of severe vitamin A deficiency (VAD)—including blindness and death. Analysis of over 150,000 children between the ages of six months and five years from several countries in which VAD is a concern indicate that almost one-quarter of early childhood deaths, especially mortalities related to diarrhea and measles, could be prevented by ensuring that children receive vitamin A (retinol) supplementation. 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 supplementation programs.

HealthTech IV Solution and Potential Impact

The RBP-EIA was developed at the request of USAID as a rapid, inexpensive test to quantify RBP from individual serum specimens, using RBP as a surrogate marker for retinol. The test is rapid; results are available in as little as 35 to 40 minutes after starting the assay. The strip wells can be read on a standard or portable EIA reader. It is designed for use in laboratories at the provincial- or district-hospital level, or by trained epidemiological surveillance teams. Application of the test will allow health care workers to assess the extent of VAD within populations, determine nutritional status, and implement the appropriate intervention. The RBP-EIA has been designed to produce data rapidly; to reduce reliance on costly, centralized laboratory facilities; and to provide an effective tool for field monitoring and recognition of VAD in at-risk populations.

Milestones and Objectives Achieved in the Past Six Months

Technical and Introduction Activities

- Received feedback from three external reviewers on "RBP-EIA: A New Approach to Assessing Vitamin A Deficiency," a resource that describes the test and its proposed use and value, and a meeting was held on June 7 at the Micronutrient Operational Strategies and Technologies Project (MOST) offices in Arlington, VA.
- Received external reviewers' final report June 27. The report finds the RBP-EIA to be a practical surrogate for serum retinol and provides suggestions for future field validation studies.
- Submitted abstract from RBP-EIA field validation study using the Cambodia data and received acceptance for International Vitamin A Consultative Group (IVACG) 2003 meeting.
- Submitted protocol to conduct field evaluation of RBP-EIA using serum and dried blood spots in Tanzania, in collaboration with researchers from the London School of Hygiene and Tropical Medicine and approved by PATH's Human Subjects Protection Committee.
- Completed the report on the proof of concept for RBP-EIA using dried blood spots (DBS) and distributed it to USAID and MOST in June 2002.
- Conducted sample degradation (handling and storage) experiments to explore the effect of temperature, freeze/thaw, and UV exposure on serum RBP-EIA. Draft report completed in October 2002 and currently under review.
- Completed draft of protocol for field validation of RBP-EIA dried blood spots and submitted to MOST for their review and comments in September 2002.

Commercialization

- Completed extensive review of manufacturers for potential commercial producer of the RBP-EIA assay.
- Identified potential manufacturer for commercial production of RBP-EIA assay—Assay Designs Inc. (ADI) based in Ann Arbor, Michigan.

- Signed materials transfer agreement and confidentiality agreement between PATH and ADI on June 25, 2002. Exchanged technical information and developed working relationship at several meetings.
- Received report from ADI titled "RBP-EIA: Summary of Experiments Run at Assay Designs, Inc." on June 27, 2002.
- Discussed with ADI draft license agreement for commercial production of the RBP-EIA.

Problems Encountered and Actions Taken

- **Problem:** Delay in Tanzania study (slated to start in October) due to delay in internal review board (IRB) clearance from Tanzania side.

  Action: PATH will reschedule the trip as soon as the clearance is complete.

- **Problem:** The external reviewers' report had a number of concrete suggestions on how to further validate RBP-EIA as a surrogate marker for retinol. They suggested:
  - Validate in three to five genetically distinct geographic settings.
  - Study the performance of monoclonal antibody in genetically diverse populations. (Can this be within a country, or does it need to be across countries? Or both?)
  - Research RBP saturation in children with infections. Need a third party lab in a developing country to evaluate both PATH and CRAFT methods.
  - **Action:** PATH is fully supportive of this activity; however, is this something that PATH should organize and support, or is this something that MOST or another third party should organize and support?

Issues: Need to identify additional collaborators and secure financial resources, and need to manufacture sufficient number of tests for validations studies in a timely fashion.

Plans for the Next Six Months

Technical and Introduction Activities

- Collaborate with MOST, CDC, and Wageningen University on additional laboratory and field validation of RBP-EIA, focusing on quality control issues for validating retinol and RBP-EIA.
- Continue further refinement of the RBP-EIA for use with dried blood spots with both venous and capillary blood samples.
- Revise the document "RBP-EIA: A New Approach to Assessing Vitamin A Deficiency" based upon external review, and develop advocacy materials for all stakeholder groups on the use of VAD testing for policy and program development and on the appropriate use of the product in the field.

- Continue the promotion of an early adopters' program to promote the introduction and appropriate use of the technology.
- Support the further development of a battery-operated strip well reader to make the test easier to use in a field setting.

Specific Validation Activities

- Conduct field evaluation of RBP-EIA using serum and dried blood spots (DBS) in Tanzania, in collaboration with researchers from the London School of Hygiene and Tropical Medicine in last quarter of 2002.
- Evaluate 1,200 DBS for RBP-EIA from samples obtained from CARE/Zimbabwe.
- Explore collaboration to validate RBP-EIA against serum retinol with University of California at Davis and Micronutrient Initiative for a micronutrient intervention research project being conducted in Senegal.
- Collaborate with Macro International to provide technical support to perform RBP-EIA on samples from the Uzbekistan Demographic Health Examination Survey, and compare to retinol assessed by high-performance liquid chromatography (HPLC).

Building Consensus Along the Way Through Field Use

- Explore collaboration with WHO through a multi-country field validation of RBP-EIA and serum retinol.
- Meet with JHU, UNICEF, and Helen Keller International to introduce the RBP-EIA and share validation results, external review comments, and to explore possible collaboration in field validation studies.

Commercialization Activities

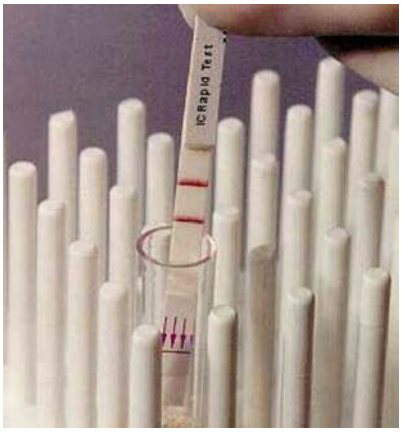
- Schedule ADI visit to PATH from October 28-30, 2002 to run "bridging experiments" to test equivalency with certain changed reagents, with the objective of developing a lower-cost test for the end user.
- Sign license agreement with a commercial entity, and make RBP-EIA commercially available for field validation studies.

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 and its high prevalence in some countries is associated with 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 3 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 IC strip test for tuberculosis, 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 HIV-positive individuals and in medically underserved populations.

Milestones and Objectives Achieved in the Past Six Months

- All of the prospective field evaluations of the TB ICS test are progressing well and final analyzed data from most of the studies should be available by the end of the year. Specific updates on each of the studies are as follows:
  - Botswana–Final analysis of the study data is nearing completion and an investigators' meeting is tentatively scheduled for December.
  - Ukraine–All of the TB suspects and healthy controls have been enrolled. Enrollment of the non-TB controls has progressed at a slower pace, but study enrollment will be completed by the end of November 2002.
  - India–Enrollment of subjects in this study is progressing very slowly, primarily due to administrative difficulties at Christian Medical College. Enrollment is expected to continue into the first quarter of 2003.
- Native and recombinant TB antigens, to serve as a potential adjunct to the Corixa antigens, have been received from Colorado State University (CSU) and evaluation of these antigens is currently underway.
- Several candidate commercialization partners have been identified. Initial assessment of the groups occurred at the American Association for Clinical Chemists meeting in July.
- A demand estimate is currently being developed as a means of quantifying the potential TB rapid test market. This information will be extremely valuable in determining tolerances in reagent, manufacturing, and final costs of the test.

Problems Encountered and Actions Taken

- **Problem:** Discussions with Corixa, regarding a license for supply of antigens for the test, continue to be extremely slow, although some progress has been made in terms of discussions about the up-front licensing fee.

  Action: It is hoped that by sharing demand estimate information along with the clinical data, Corixa will become more amenable to timely discussions.

Plans for the Next Six Months

- Complete patient enrollment and data entry at study sites in Ukraine and India.
- Analyze the data generated at each of the sites and prepare a final report on the performance characteristics of the test. If the performance of the test is satisfactory, the team will proceed with transferring the technical know-how for commercial production. Thereafter, a detailed plan for successful introduction of the test will be developed. However, if the data does not meet the necessary performance criteria, particularly in HIV positive populations, a meeting with USAID and TB experts will be initiated. This meeting will assist the team in deciding whether or not to continue research and development activities on a test suitable for use in HIV prevalent populations, and to discuss the utility of the current test in HIV negative populations.
- Continue to evaluate the native and recombinant antigens received from CSU.
- Continue to work with Corixa to finalize the supply agreement for the antigens.
- Continue to perform due diligence screening of potential test manufacturers.

Immunochromatographic Strip Test for Gonorrhea

Health Need Addressed

Despite long-standing, global public-health efforts to control sexually transmitted diseases (STDs), *Neisseria gonorrhoeae* (gonorrhea) infections still occur in epidemic proportions in the developing world and in specific regions of the United States. For effective control of gonorrhea, 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 for the control of HIV/AIDS transmission.

HealthTech IV Solution and Potential Impact

The IC strip test for gonorrhea (GC), developed under HealthTech III, utilizes relatively inexpensive, off-the-shelf components and is formatted to identify a specific gonoccocal 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 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 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 Objectives Achieved in the Past Six Months

- Two separate production lots of the PATH GC IC strip test were submitted to WHO's Sexually Transmitted Diseases Diagnostics Initiative (SDI) for inclusion in a laboratory-based evaluation. The performance of the PATH test was compared to two other rapid GC tests—Binax's (Portland, Maine, USA) IC strip test and ThermoBioStar's (Boulder, Colorado, USA) Optical Immunoassay. The data from this study was ambiguous, as the PATH test apparently had the lowest analytical sensitivity, and yet all of the tests had equally poor performance with archived specimens. The GC IC team is currently attempting to obtain more information from the WHO SDI on the testing protocol.
- The prospective field evaluation of the GC IC strip test in Johannesburg, South Africa, is progressing very well. Enrollment of male subjects has been completed and data analysis is underway. Fifty percent of the female subjects have been enrolled, and it is anticipated that final enrollment would be completed by the end of December.
- PATH staff recently met with representatives from ThermoBioStar to discuss, in detail, the supply agreement for the GC antibody reagents.
- A global demand estimate model for GC tests has been developed. This information will be critical in determining the tolerances on reagent, manufacturing and final test costs.
- An additional field site for further evaluation of the performance of the test in asymptomatic women has been identified in Bangladesh. If the performance data of the test in South Africa is satisfactory, an additional prospective study will be coordinated to further assess test sensitivity and specificity, as well as to look at operations research parameters.

Problems Encountered and Actions Taken

- **Problem:** Collaboration with the proposed research group in the Philippines has been problematic.

  Action: For this reason, an additional, well-qualified site has been identified in Bangladesh. If the data from the South African study are satisfactory, it is anticipated that patient enrollment in Bangladesh would begin in January 2003.

Plans for the Next Six Months

- Initiate discussions with the WHO SDI to better understand the process used to evaluate the rapid GC tests.
- Complete patient enrollment and data analysis in the South African field evaluation trial.
- Conduct the following, if performance data from the South African study is satisfactory:
  - Finalize the research protocol and obtain ethical clearance for the study in Bangladesh.
  - Finalize and sign the collaboration agreement with ThermoBioStar. Work with ThermoBioStar to develop the licensing structure with a commercial partner.
  - Finalize selection of a commercial manufacturer for the test and transfer the technical know-how for production.
  - Develop a detailed product introduction plan.

- Submit data generated in the South African study for publication in a peer-reviewed journal.
- Initiate a meeting with USAID and STD experts if the clinical performance of the test is not satisfactory. This meeting will assist the team in deciding whether or not to continue research and development activities.

Immunochromatographic Strip Test for Chlamydia

Health Need Addressed

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

HealthTech IV Solution and Potential Impact

The IC strip 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 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 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 Objectives Achieved in the Past Six Months

- Current research and development efforts have identified the probable cause of the reduced sensitivity in the study conducted at the University of Alabama in 2001. Laboratory activities for improving the sensitivity and overall robustness of the assay are progressing well.
- A series of experiments are being conducted to examine the effect of various assay components on the overall performance of the test. The intended samples to be used with the test are urethral and endocervical swabs, but it is hoped that the assay will be sufficiently sensitive to use first void urine from men and vaginal swabs from women.

Problems Encountered and Actions Taken

None at present.

Plans for the Next Six Months

- Once acceptable analytical sensitivity and specificity with the improved prototype has been obtained, the CT ICS test will be retrospectively evaluated using endocervical swab samples and male first void urine samples collected during the gonorrhea prospective evaluation in Johannesburg, South Africa.
- Assuming adequate retrospective clinical performance, the test will be prospectively evaluated in a clinical evaluation. Potential sites in India and Bangladesh have been identified.

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 IC strip 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 Objectives Achieved in the Past Six Months

- Launched the rapid diagnostics web site that includes information on malaria rapid tests and a list of commercial manufacturers and distributors.
- Assisted WHO in Manila with the development of protocols for quality assurance of rapid malaria tests.
- Purified the cloned monoclonal antibody supernatants and screened the three monoclonal antibodies in the IC strip test format. Preliminary data, using a small number of clinical samples, indicates that the purified monoclonals are sensitive and specific to HRP-II. Further evaluation is needed with a larger number of control samples, and the threshold detection level of the assay needs to be determined.

Problems Encountered and Actions Taken

None at present.

Plans for the Next Six Months

- Continue laboratory-based evaluations of the three monoclonal antibody reagents in the IC strip 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 is 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 laboratories tests that can be done on dried blood spot samples could potentially solve the problem of transporting lab 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. PATH is specifically interacting with the USAID-supported 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 Objectives Achieved in the Past Six Months

- Participated in meetings in Washington, D.C., with USAID, PHR+, CDC, and Tanzanian health officials on development of a HIS in Tanzania.
- Held meetings with Murray Trostle of USAID to discuss PATH's possible role in USAID-funded work on HIS and negotiated funding.
- Attended the USAID symposium on "Thirty Years of Population and Health Data Collection."
- Participated in a meeting at CDC in Atlanta with USAID, PHR+, and CDC staff on defining roles for partner agencies working on a HIS for Ghana.
- Prepared a spreadsheet of commercially available rapid diagnostic tests or central laboratory tests that can or might be adapted to work with dried blood samples for diseases of interest in Ghana.
- Repeated follow-up with Abt Associates and the Academy for Educational Development in planning assessment visits to Ghana and Tanzania.

A busy health post in Uganda

Problems Encountered and Actions Taken

- **Problem:** CDC is resistant to the use of rapid tests for definitive diagnoses of outbreak-prone diseases.

  Action: HealthTech will have to provide extensive published evidence for the accuracy of any tests that we recommend.

- **Problem:** CDC and PHR+ are the major partners in this project and HealthTech has a much smaller role (and budget) and is joining a work in progress.

  Action: HealthTech will need to create a clear niche for our work and establish our credibility and usefulness to the goals and objectives of our larger partners.

- **Problem:** None of the partners has followed through on their plans to include PATH in an assessment visit to either Tanzania or Ghana.

  Action: PATH may have to work with USAID to organize an independent visit.

Plans for the Next Six Months

- Organize visits to Ghana and Tanzania to gauge the interest and possible uses for improved diagnostic testing in their respective HIS.
- Develop a work plan and budget based on the assessments done in both countries.

Rapid Diagnostics Web Site

Health Need Addressed

Health program planners, managers, and laboratory staff need clear, well-documented information to make the best decisions about diagnostic test choices for resource-poor settings. Because they are a relatively new group of technologies, information on rapid diagnostic tests is difficult to find in one place. PATH regularly receives email inquiries about the availability and appropriate uses of rapid diagnostic tests.

HealthTech IV Solution and Potential Impact

Based on our experience in test development and introduction, PATH staff have developed a rapid diagnostics test web site that brings together information on types of available test technologies, the accuracy of these tests, their appropriate uses, and contact information for their purchase. The potential impact of this web site is better diagnostic test choices by program planners, managers, and laboratory staff as well as the promotion of rapid tests in general.

Milestones and Objectives Achieved in the Past Six Months

- Completed the development of the site and launched it for use, using various publicity approaches. Site use data shows a steady increase in usage (www.rapid-diagnostics.org).

Problems Encountered and Actions Taken

- **Problem:** It is difficult to keep manufacturer information up-to-date.

  Action: HealthTech will update this information twice annually.

- **Problem:** Funding for continuous maintenance of the site is uncertain for updating and expanding the site.

  Action: PATH will look for other sources of funding.

Plans for the Next Six Months

- Continue implementation of introduction activities to promote the site.
- Respond to inquiries based on site content.
- Monitor site use.
- Initiate update of material and links at the end of six months.

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 four percent at the end of three years. An improved method incorporating vas occlusion using cautery could provide a technique with increased efficacy and reasonable cost.

HealthTech IV Solution and Potential Impact

Currently, FHI and EngenderHealth (EH) are collaborating on a study to determine if there are clinical advantages to vasectomy using cautery and to determine safe and dependable procedural methods to use in conjunction with cautery. In addition to this field research, PATH would evaluate the physical durability and the potential for reuse of a thermal cautery device. The long-term goal of this collaboration would be to introduce a cautery vasectomy technique, in conjunction with recommended procedural and reuse methods, for introduction into low-resource settings.

Milestones and Objectives Achieved in the Past Six Months

- Developed a limited scope of work that could be accomplished by PATH within FHI and EH's clinical trial timeline.
- Developed testing protocols to provide a preliminary evaluation of the cautery device's functional potential for reuse in limited-resource settings as well as provide a brief summary of the device's general usability issues.
- Completed this evaluation and reported the results in a timely fashion to FHI and EH.

Problems Encountered and Actions Taken

In terms of PATH's involvement with this project, no significant problems have been encountered.

Plans for the Next Six Months

- FHI and EH are currently conducting studies to determine if vasectomy by thermal cautery offers clinical advantages and greater success compared to ligation/excision methods.
- If the above is found to be true, FHI will attempt to demonstrate the feasibility and cost-effectiveness of a thermal cautery for use in low-resource settings.
- In order to reduce the cost of cautery, PATH will lead the evaluation of a selected cautery tip for safe resterilization and reuse.
- If reuse is found to be appropriate and safe, PATH and FHI will work together to develop procedures for reuse of cautery tips in the field, including cleaning and sterilization methods.

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 cord-care kit designed for use in home births. Based on a needs assessment in rural community settings in Nepal, the purpose of the kit is to provide items that will encourage clean delivery practices. The contents of the kit developed in Nepal include pictorial instructions, a small bar of soap, a polyethylene delivery sheet, a cord-cutting surface, cord ties, and a clean razor blade. 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 Objectives Achieved in the Past Six Months

- PATH continues to distribute the *Basic Delivery Kit Guide* to individuals and institutions around the world. Approximately 90 new copies were shipped out in the past six months, for a total of nearly 500 since publication.
- PATH staff submitted an article entitled "Acceptability and Use of Clean Home Delivery Kits in Nepal: a Qualitative Study" to the international *Journal of Health, Population and Nutrition* in August 2002.
- Under a HealthTech subagreement, the Ministry of Health (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 2002:
  - The study team conducted regular supervision visits in the study areas, and in May though June they organized refresher training for the village health workers.
  - Qualitative research activities were initiated in July 2002. The study team trained two research assistants in qualitative research techniques and conducted 17 in-depth interviews according to the respondent categories outlined in the study protocol.
  - The seventh cluster out of a total of ten clusters was enrolled in the study on September 30, 2002.

Problems Encountered and Actions Taken

- **Problem:** Difficulties in local transport in the Tanzania delivery kit evaluation.

  Action: Problems were resolved through the purchase of bicycles and collaboration with CARE and NIMR for use of their motorbikes and vehicles.

- **Problem:** Due to a delay in project start-up activities in Tanzania, and the need for the study to extend to account for the last enrolled mothers to give birth and be interviewed, the study calendar was inaccurate.

  Action: PATH worked diligently with the local partners to design and agree upon a plan for a nine-month extension and allocate necessary funds to accommodate the new timeline. This did involve an increase in the budget from HealthTech.

Plans for the Next Six Months

PATH will continue to provide technical assistance to the MOH and NIMR to conduct a combined quantitative/qualitative evaluation of the single-use UNFPA delivery kit in Mwanza, Tanzania.

Development of a Vaccine Against Human Schistosomiasis

Health Need Addressed

Schistosomiasis affects approximately 200 million people worldwide, and over 85 percent of these 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. It is also 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 to diagnose (and expensive compared to the cost of treatment). There is no specific symptom when infected, and yet the long-term consequences are devastating. A vaccine capable of protecting children from infection would be a tremendous tool for the control of this disease. The 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 financially 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, through HealthTech III and IV, PATH was responsible for project and administrative management, procurement, training and travel arrangements, intellectual property rights issues, and sub-contracting the services required from both the HSPH and Bachem.

Milestones and Objectives Achieved in the Past Six Months

- The SVDP project ended September 30, 2002.
- Dr. Alan Fenwick, advisor and management specialist, left Cairo in May, thus completing his contribution as resident project manager.

Problems Encountered and Actions Taken

No problems were encountered during this time period.

Plans for the Next Six Months

- USAID will determine whether or not to extend the SVDP project another year.
- If the project is extended, the project will coordinate training in human subjects research review procedures for the Egyptian members of the SVDP Internal Review Board.
- A new project will be developed to ensure continuation of the ERDC contribution to the battle against infectious diseases in Egypt.