Sustainable Transfer of Biotechnology to Developing Countries

Fighting Poverty by Bringing Scientific Tools to Developing-country Partners

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Poverty and social inequalities have powerfully sculpted not only the distribution of infectious and other diseases but also the course of disease in those affected. The lack of proper diagnosis and access to adequate health services only compounds the problem. In low-resource settings, the burden of disease can be reduced if the basic human and material resources exist to support the use of low-cost interventions by appropriately trained personnel. For 20 years, the Sustainable Sciences Institute has built scientific capacity in developing countries to recognize, prevent, and respond to the threats posed by disease.

Key words: **technology transfer; infectious disease diagnosis; information and communication technologies; sustainable science in developing countries**

Infectious Diseases and Poverty

Infectious diseases are still a major cause of death, disability, and social and economic upheaval for millions around the world. More than 90% of the deaths from infectious diseases worldwide are caused by only a handful of diseases (lower respiratory infections, human immunodeficiency virus [HIV]/AIDS, diarrheal diseases, tuberculosis, malaria, and measles). And although not major killers, several of the world's neglected infectious diseases (e.g., lymphatic filariasis, leishmaniasis, trachoma, intestinal parasites, leprosy, and onchocerciasis) cause chronic disability and stigma for millions. Also, reemerging diseases, such as dengue and multidrug-resistant tuberculosis, represent great burdens to the health systems of poor nations.[1] Illness and death from infectious diseases are particularly tragic because for the most part they are preventable or treatable. Even though infectious diseases cause 59% of mortality in developing countries, a rate that is at least 80% higher than that in industrialized nations, only 5% of the global health research funding is directed to investigating the diseases that affect 90% of the world's population.[2]

Social and economic factors, in addition to the general ecology of developing countries, contribute to the high rates of infectious disease. Poverty, lack of access to health care, shifting human migration patterns, emerging viruses and antibiotic-resistant bacteria, increased development activities, and environmental destruction all contribute to the expanding effect of infectious diseases. Poor living conditions and overcrowding make those living in poverty especially vulnerable to communicable diseases. Treatable infections are fatal for the poor with only limited access to health care and medicines, while malnutrition and compromised immune systems are key risk factors for several major diseases, including HIV/AIDS and tuberculosis.[3] Not surprisingly, the poorest and most vulnerable are the most severely affected by infectious diseases, and children and women are especially susceptible to their effect. Children in developing countries, already lacking proper nutrition, may also lack access to affordable vaccinations that prevent childhood illnesses or to simple interventions for diarrheal diseases; in addition, malaria and HIV are increasingly affecting this age group.[4]

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The repercussions of infectious diseases go well beyond morbidity and mortality statistics. Poverty not only defines the circumstances in which infectious diseases thrive, but the cycle of poverty is exacerbated by lost productivity, missed educational opportunities, and excessive health care costs for the affected and their families. Societies and communities bear the economic burden of caring for those who are sick. Scores of orphans, uneducated generations, and child-led households are another terrible consequence of these diseases.[5]

We believe that even in low-resource settings, the burden of infectious disease can be reduced if the basic human and material resources exist to support the use of low-cost interventions by appropriately trained personnel. Effective disease control is possible but will become a reality only when every nation, regardless of size, location, or wealth, has the capability to recognize, prevent, and respond to the threats posed by infectious disease. The mission of the Sustainable Sciences Institute (SSI) is to facilitate this process.

Background: SSI's Genesis

In 1988, the Applied Molecular Biology/Appropriate Technology Transfer Program (AMB/ATT) was first conceived. Eva Harris, a recent Harvard graduate, envisioned such a program while volunteering in 1988 in war-torn Nicaragua, at the Centro Nacional de Diagnóstico y Referencia (CNDR) of the Ministry of Health in Managua. Harris was struck by the lack of resources available to her Nicaraguan peers in terms of research funding, equipment, supplies, training, and technical advice, as well as by the challenges posed to scientists by poverty and everyday life with suboptimal infrastructure, infrequent running water, and intermittent electricity. Despite these barriers, she was successful in training local scientists in the implementation of molecular biology techniques for the diagnosis of infectious diseases. She did so by deconstructing the technologies in question into their basic principles and building them back onsite while adapting them to the local conditions.

Harris also witnessed the effect of poverty, war, and the lack of access to diagnosis and health care on infectious diseases in Nicaragua and realized that, to improve the public health situation, the human and public health resources first had to be strengthened. During her graduate school years in the Department of Molecular and Cell Biology at the University of California, Berkeley, she partnered with like-minded scientists and formed alliances with colleagues in the United States and abroad who were interested in building scientific and public health capability in developing countries. This group of young, progressive researchers craved the chance to teach and apply their scientific knowledge in a way that would make a concrete difference in the lives of developing-country residents. For 10 years, they did so through the AMB/ATT program, following Harris's initial vision, by donating their time and seeking small grants and individual donations.[6–8] Through conducting customized training workshops and simplifying technologies onsite, they taught molecular biology-based disease diagnosis, epidemiology, and control of infectious diseases to public health researchers and educators in Nicaragua, Ecuador, Bolivia, and Guatemala. They also channeled hundreds of thousands of dollars' worth of donated laboratory equipment, supplies, and reagents to Latin American researchers and institutions. Importantly, they formed lasting partnerships with many trainees, which have been crucial to sustain the initial mission over time.

In 1997, Harris was awarded a MacArthur Genius Fellowship for this work. With this funding and support from small foundations, family, and friends, in September 1998, SSI was founded in San Francisco, CA. SSI is a 501(c)(3) nonprofit organization that assists developing-country public health professionals by supplying the training, funding, equipment, supplies, networking, and technical advice that they need. It also manages several scientific and public health programs in Nicaragua and Egypt. SSI is a medium-size nonprofit organization, with a staff of six in the San Francisco office; a subsidiary in Managua, Nicaragua, with 25 employees and another in Cairo, Egypt; a highly active Board of Directors (with 11 members); and a prestigious Advisory Council. SSI also operates with the assistance of many organizational volunteers and more than 100 active scientific volunteers.

More than 70% of SSI's operational budget of approximately $1 million per year is contract revenue, where SSI partners with funders to manage specific research and public health activities in developing nations. The capacity-building program, SSI's staple activity, is supported largely by foundations and individual donors who believe in its mission.

SSI's Capacity-building Program

SSI was created in response to the needs of public health researchers in developing countries. The basic premise is that by building local scientific capacity and human resources, one can help control and

prevent infectious diseases and improve public health infrastructure and the health status of the population. Through education, training, and support of locally relevant scientific projects, SSI seeks to leverage the resources of the developed world to enhance the capacity and encourage the ingenuity of researchers in the developing world. By building local health research capacity, developing country researchers are empowered to reduce the burden of poverty and disease in their communities. SSI currently operates throughout Latin America and Egypt and is exploring opportunities to expand its outreach to Africa and Asia.

As of 2007, SSI and its precursor, AMB/ATT, have conducted 50 workshops and trained more than 1200 researchers from 20 different countries in various state-of-the-art techniques for cost-effective diagnosis and epidemiological analysis of relevant infectious diseases, as well as in grant preparation and manuscript writing. Another 1500 scientists have attended seminars and conferences during the workshops. SSI's scientific capacity-building program has a four-pronged approach: workshops, material aid, small grants, and networking.

Workshops

The workshops are modeled after the AMB/ATT principle and over the years have morphed to respond to the changing needs of the trainees. The basic concept is a free, hands-on, in-country, 1- to 2-week training workshop involving 20–25 participants from several national and/or regional institutions. The training modules consist of laboratory techniques (diagnostic and basic research); epidemiological skills; manuscript writing; grant writing; and more recently, ethical issues in research (bioethics). Modules on bioinformatic tools for DNA sequence analysis and the use of information technologies for public health are currently being piloted.

The workshops respond to the needs of the researchers and are coordinated by SSI's Scientific Director from the San Francisco office, who works with a local counterpart on the organization and logistics. Participants are selected onsite per SSI's guidelines and usually include young scientists and public health workers with laboratory and research exposure who work directly on programs and in institutions with local influence. At the workshops, the participants work in small groups, each with an experienced tutor, who is often a former trainee from another country in the region or a U.S.-based scientist (particularly in the manuscript-writing workshops). Peer trainers are previous SSI trainees who have continued to excel in the field and have mastered SSI's instruction theory and methods to become workshop instructors. This South-South transfer, or peer training, is an extremely effective approach to regional capacity building. Learning from researchers who are working successfully under similarly resource-constrained conditions generates trust and greater empowerment for trainees, who realize that their obstacles are not insurmountable or unique. Regionally based instructors are also more attuned to the environmental and sociocultural challenges that participants face and can convey the necessary information for meeting those challenges in a culturally appropriate manner. Also, the approach creates a multiplier effect by training local instructors who go on to provide further training as part of future SSI peer-training workshops as well as self-organized trainings at their home institutions and throughout their country.

For the laboratory workshops, the local host institution usually has basic infrastructure in place, and SSI provides the equipment, tools, and reagents needed during the workshop and enough materials to implement the technology after the course. SSI adapts the technologies to the local conditions and infrastructure, taking site-specific limitations into account. In most laboratory-based workshops, diagnosis of priority infectious diseases and typing of pathogens are taught, responding to the request of the local counterparts in terms of which specific techniques are lacking and which infectious diseases to focus upon. Basic epidemiological skills and tools for statistical analysis are also taught in separate or accompanying modules.

Over the years, SSI's workshops have led to the identification of the etiology of new outbreaks of dengue, leptospirosis, cholera, leishmaniasis, malaria, and tuberculosis throughout Latin America and of hepatitis C in Egypt, and they have helped provide local public health officials with the evidence needed for pertinent and timely actions for control and containment. The workshops also permit the generation of preliminary research data that local scientists use in grant proposals.

SSI's grant-writing module focuses on providing general grant-writing skills and practical ideas to increase the likelihood of obtaining funding. The sections in a successful grant—abstract, specific aims, background and significance, preliminary results, research design and methods (including anticipated results and potential problems), timeline, budget and budget justification—are reviewed in depth. Participants break into small groups to work on actual proposals that use their preliminary data, often generated during the laboratory workshop. Internal Review Boards, human subject protocols, and letters of consent, as well as scientific collaborations and potential

funding sources, are also discussed in detail. Many proposals generated during the workshops are then submitted to SSI's Small Grants program and reviewed by scientific volunteers. Participants can also take advantage of SSI's volunteer network for pre-review of their proposals to strengthen their applications.

The manuscript-writing workshops originated in direct response to the needs of SSI's previous trainees and other developing-country scientists who over the years had successfully conducted research and accumulated data and relevant information that could be published in local and international scientific journals. Unfortunately, researchers in the least developed countries are often excluded from funding opportunities since they are not considered of sufficient scientific stature because they generally do not publish their findings. Few developing-country investigators receive training in how to convert their work into manuscripts for publication or have the means, motivation, or the time to do so.

Thus, the objective of SSI's manuscript-writing workshops is to provide the skills needed to transform existing data into publishable material and to increase the likelihood of a manuscript's being accepted for publication in a reputable scientific journal. Publications boost trainees' scientific visibility in the international community, help them gain ownership of their research, and improve their chances of competing successfully for external funds. Also, the findings in published manuscripts have the power to inform and influence local and regional public health actions. For the workshop philosophy, SSI relies on the same concept as in the laboratory and grant-writing courses. The scientific manuscript is deconstructed into its universal components—title, abstract, introduction, methods, results, discussion, and references—and is discussed in detail, with examples of what the content of each section should be. The journal selection, submission, review, and publication process is covered, illustrated with specific examples. Issues about the responsibilities, criteria, and ethics of authorship are discussed as well. Each afternoon, the 15–20 participants have the opportunity to work one on one with an experienced scientist to analyze the data they have generated and to produce a preliminary manuscript before the end of the weeklong workshop. This initial version is later revised by SSI volunteers around the world, who serve as editors, to improve the chances for publication. SSI's manuscript-writing workshops have attained great popularity throughout Latin America and Egypt, and this enthusiastic response indicates that SSI is indeed fulfilling an unmet need.

As researchers become more proficient and engaged in projects that involve the participation of the community, ethical issues arise regarding research with human subjects, informed consent, genetic research and DNA, and a study's responsibility to the community. To bring awareness to these issues, SSI has developed a new workshop module in collaboration with Drs. Richard Cash and Dan Wikler at Harvard University, the first of which was conducted in Nicaragua in 2007. Participants are made aware of the ethical dilemmas facing researchers and receive knowledge that will enable them to make decisions or influence local decision making about the ethical issues that affect their research and their communities.

SSI is currently developing new training modules responding to the interests and needs of researchers around the globe. A bioinformatics and sequence analysis module will focus on training in the tools necessary for accessing available DNA sequences in public-domain databases on the Web and on the use of specific programs for sequence and phylogenetic analysis. It will also provide participants with collaborations and partnerships to enable generation of DNA sequences of local relevance. This module has emerged from the increasing importance of genomics in diagnosis and monitoring of infectious diseases and from the need for researchers in the developing world to have the tools in hand to track diseases in real time, identify their etiology and molecular phylogeny, and contribute this information to aid in global public health and the control of epidemics and pandemics.

Finally, a workshop module is being piloted on information and communication technologies (ICTs), such as personal data assistants (PDAs), geographic information systems (GIS), barcodes, fingerprint scans, computerized registries, cell phones, and voice over IP (e.g., Skype) for application in public health settings. This workshop concept has received great interest for its versatility and application in clinical studies and trials, community-based research studies, improving immunization efficiency and access to health services, and facilitating compliance of laboratories and clinics with quality-control exigencies (e.g., Good Clinical Practices [GCP] and Good Laboratory Practices [GLP]).

Material Aid, Small Grants, and Networking

The Material Aid program is key to SSI's capacity-building efforts. SSI has contacts with many U.S.-based institutions, companies, and universities that donate materials, supplies, and minimally used equipment or provide deep discounts and donations of reagents. The material is then sent to collaborators and past SSI trainees throughout Latin America in response to their

specific requests. For many scientists, these donations have been crucial for starting up their laboratories or have allowed them to continue with critical work. Over the years, SSI has donated hundreds of thousands of dollars' worth of equipment and material that has received a new lease in resource-poor countries instead of going to waste.

SSI's small grants are another important component of the capacity-building concept. Once or twice per year, SSI releases a call for research proposals for funding consideration and invites recent trainees who have drafted proposals during the workshops to apply. At SSI's grant-writing workshops, SSI's instructors assist participants to generate high-quality research proposals, using appropriate methodological and technical frameworks with solid plans for analysis. Following an application and review process based on those used by the National Institutes of Health and the World Health Organization (WHO) Tropical Disease Research Unit, and depending on scientific merit and public health relevance, three to five proposals receive funding of $6,000–$12,000. SSI's program strategy recognizes that a small injection of seed money can have a large effect on developing countries, where research funds are extremely scarce. For example, a few thousand dollars can cover the salary of a scientist, necessary supplies, and the cost of administering questionnaires to a local population. SSI grants ensure that the success of the workshops translates into the implementation of a research project. SSI provides oversight, technical advice, and supplies needed throughout the project. This program thus strengthens the capabilities of individual scientists and communities of investigators so that they will be better prepared to continue research after the SSI project-funding period. Ultimately, most of the results from SSI-funded work are published in scientific journals and form the basis for further investigation and public health applications.

Finally, SSI facilitates networking among scientists locally, regionally, and internationally, and between local researchers and relevant institutions, such as the Pan American Health Organization, WHO's Tropical Disease Research Unit, Netropica, the Program for Appropriate Technology in Health, and the Centers for Diseases Control and Prevention, to foster dialogue, decrease scientific isolation, increase funding possibilities, and improve concerted efforts in handling outbreaks or epidemics within and across borders.

Technology Transfer

SSI is particularly concerned about the lack of resources available to scientists and health workers in poor countries who as a result cannot recognize and resolve infectious disease and other basic health problems at the local level. This issue is especially urgent because half of all deaths in the developing world are due to infectious diseases. And although the technologies and resources to reduce the effect of these diseases exist, they are unavailable where they are most needed. SSI seeks to bridge this gap by helping biomedical scientists and public health workers gain access to appropriate training, equipment, and supplies.[9] Not only does SSI demystify techniques by helping researchers understand their fundamental principles and deconstructing components into individual steps or reagents, but it also fosters the natural creativity that researchers forced to work in suboptimal conditions and with limited resources have mastered. With this in mind, during SSI workshops, participants learn how to use substitutes for expensive lab equipment and invent alternative methods. For example, a thermocycler, a machine that generates temperature cycles necessary to perform the polymerase chain reaction (PCR)—now a ubiquitous method for amplification of nucleic acids that is used for research and diagnostic purposes and costs $6,000–$10,000—can be replaced by simple water baths. Expensive silica gel used in DNA isolation can be substituted by ceramic powder bought in bulk from a builder supply store. From a record turntable a shaker can be constructed; a soda bottle can serve as a container to grow bacteria; and an old kitchen blender can be transformed into a centrifuge.[10] Similarly, reagents labeled as "Solution A" or "B" in a particular kit can be made inexpensively by understanding the origin and purpose of the reagent and accessing the original publication that explains the protocol and recipe for the mystery solution.[11]

If a technology is truly not appropriate for existing conditions, SSI discourages its implementation. Often new technologies represent a large investment in time and funds, and although an institution might have resources to purchase the equipment, it often lacks the ability to sustain it long term. These resources can instead be channeled to more significant applications or to strengthen existing technologies. For example, purchasing a sequencing apparatus might not be the best means to obtain the DNA sequence of local samples if its use is minimal. Partnering with SSI, or with other researchers in more developed countries, to access a DNA sequencing service might be a more appropriate and inexpensive alternative. The sequencing technology on its own is not what is relevant; more important is to have the tools and training to enable generation of relevant DNA samples and to analyze the sequences obtained to use the resulting information in a

significant manner. SSI's goal is to put tools and knowledge in the hands of researchers and professionals, combined with suggestions on how to address basic research or local health problems.

From Workshops to Centers of Excellence

Over the last few years, SSI has modified its approach to training to increase its gains and its sustainability. Because SSI now has long-term connections with developing-country researchers who have shown commitment to their communities and exceptional performance, we have chosen to continue to facilitate their development into leaders in their field by providing them with support in all aspects of the scientific discipline as well as ongoing material aid and mentoring. As a result, in addition to training several new groups of scientists each year, SSI is committed to providing effective, long-term support to a few institutions and researchers in Latin America and Egypt working in discrete geographic areas with high disease burdens. With this approach, SSI avoids spreading its limited resources too thinly over many regions and instead concentrates resources by supporting outstanding researchers and institutions with the goal of developing them into Centers of Excellence.

This concept was modeled after SSI's success over two decades of support and collaborations with the Nicaraguan Ministry of Health, which has led to programs with outcomes that significantly affect public heath. With this vision, SSI returns to a selected group of trainees throughout the region and brings new technologies, knowledge, and material aid to strengthen their research capacity. In addition to the groups in Managua, Nicaragua, we have fostered Centers of Excellence in Guayaquil, Ecuador; Medellin, Colombia; Lima, Perú; and Panama City, Panama. All these places have established state-of-the-art laboratories supported by SSI and are national or regional reference laboratories for various infectious diseases.

A Long-term Approach: The Nicaraguan Success Story

Whereas some organizations and researchers practice a "parachute" approach to global health by appearing in a developing country when an important disease outbreak arises, fixing the problem if possible, and leaving along with the knowledge and biological samples, at SSI we have taken a different approach. We provide researchers with long-term support, during both emergencies and calmer times, and form long-lasting partnerships and collaborations. SSI's step-by-step approach to collaborations with Latin American and Egyptian scientists is such that the main goal is to develop scientific capacity while supporting top-level investigations of locally relevant problems that lead to high-quality publications and improve the health of local communities. This bottom-up, or grassroots, approach produces gains first at the level of individual scientists and small groups that then expand to institutions and government agencies.

The best example of the success of SSI's approach is in Nicaragua. A long-term partnership has been sustained for more than 20 years among SSI (previously AMB/ATT); investigators at the University of California, Berkeley, where Harris is an Associate Professor and Coloma, a Senior Researcher; and colleagues at the Ministry of Health in Nicaragua. Harris began collaborating with the Ministry of Health's CNDR in 1988, and it was the site of the first training workshop by the AMB/ATT program in 1991. Since then, Nicaraguan scientists have been trained in molecular diagnostics and epidemiology, cellular immunology, classic epidemiology and biostatistics, cell culture and virus isolation, and cutting-edge research methods in many infectious diseases. The collaboration with the Department of Parasitology began in 1988, first with support of biochemical and immunological diagnostic and typing methods and then with the introduction of simplified PCR techniques for the diagnosis and characterization of leishmaniasis, which have been used routinely for the last 17 years.[12] New molecular typing methods were also developed,[13] and use of these assays in-country led to the discovery of a new form of disease caused by *Leishmania chagasi* infection in Nicaragua (atypical cutaneous leishmaniasis [ACL]).[14] Further studies examining the parasitological, immunological, epidemiological, and entomological characteristics of ACL were conducted, and the Ministry of Health incorporated information about recognition, diagnosis, and treatment of ACL into posters that were distributed throughout the nation's health centers. The Ministry of Health also purchased increased amounts of the indicated therapeutic agent, thereby making treatment readily available.

Our overall approach as been to strengthen laboratories, hospitals, and health centers through research collaborations that address scientific as well as clinical and operational questions of local importance. One of the best illustrations involves dengue, the most important mosquito-borne viral disease affecting humans. Four serotypes of dengue virus are transmitted

to humans by mosquitoes and cause a spectrum of disease manifestations, from an acute, self-limited febrile illness to the life-threatening dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), characterized by increased vascular permeability, low platelet count, and hemorrhagic manifestations. Dengue fever and the more severe DHF/DSS have emerged as major public health problem, particularly in Southeast Asia and Latin America, with 3 billion people at risk, 50 million dengue fever cases, and 250,000–500,000 cases of DHF/DSS estimated annually.[15] Over the years of collaboration with SSI and UC–Berkeley, members of the Department of Virology in the CNDR at the Nicaraguan Ministry of Health have mastered all the state-of-the-art techniques for the diagnosis and characterization of dengue virus. They have developed in-house diagnostic kits to replace expensive commercial versions, as well as new molecular typing techniques and field methods such as detection of dengue virus–specific antibodies in saliva or filter paper blood samples.[16–19] Importantly, in addition to their use in research studies, these methods have been incorporated into the routine surveillance of dengue, both at the central reference laboratory and regional laboratories, resulting in improvement of epidemiological surveillance at a national level. In 1995, Ministry of Health researchers used new molecular techniques to rule out dengue virus as the cause of an outbreak of hemorrhagic fever in northern Nicaragua. Later, international teams of scientists identified the *Leptospira* bacterium as the culprit, and antibiotics were distributed. Management of this epidemic was critically dependent on the ability of the local Nicaraguan researchers to initiate a rapid and reliable scientific investigation. In addition to serological, virological, and molecular biological diagnostic methods, the Nicaraguan National Virology Laboratory has become proficient in more sophisticated techniques, such as the plaque reduction neutralization test, amplification of the full-length dengue viral genome, and quantitation of viral load with real-time PCR. As a result of strengthening the Virology Laboratory, the Nicaraguan CNDR is recognized as a Center of Excellence for dengue in Central America, and members regularly serve as consultants and instructors in regional workshops on dengue diagnosis and epidemiology.

This expertise has spread beyond the field of dengue. Once the concept of molecular diagnostics and characterization had been introduced through the initial AMB/ATT–SSI workshops, CNDR researchers immediately began implementing other applications. For example, the Department of Virology has expanded their capacity in PCR-based diagnosis and typing to influenza A and B, respiratory syncytial virus, parainfluenza and other respiratory disease viruses, as well as hepatitis C, enteroviruses, HIV, and HIV viral load. Other departments have implemented PCR-based diagnostics for chlamydia, gonorrhea, leptospirosis, and other diseases. The CNDR has established a state-of-the-art molecular biology unit to facilitate this work and maintain high-quality performance.

In addition to strengthening laboratory capacity, collaborative studies on dengue have been conducted in the Nicaraguan National Pediatric Reference Hospital since 1998 that address both scientific questions (e.g., host and viral risk factors for severe disease) and clinical questions of local relevance (e.g., ultrasound as a noninvasive diagnostic and prognostic tool to detect plasma leakage, the hallmark feature of DHF/DSS; changes in fluid administration that greatly improve case management of dengue patients; reevaluation of the dengue case classification scheme).[20–25] Enormous improvements in quality control, data management, and sample handling have enabled participation in international multicenter studies that include clinical monitoring as well as collaborations to address sophisticated scientific questions such as host gene expression responses using microarray and proteomic methods, identification of infected cell types through multicolor flow cytometry, and evaluation of viral intrahost diversity by single-molecule full-length sequencing of the dengue viral genome. Importantly, these studies have led to the establishment of a longstanding collaboration among laboratory, epidemiology, and clinical sectors of the Nicaraguan health system that have traditionally functioned in isolation.

One of SSI's greatest achievements in Nicaragua was the incorporation of a subsidiary in Managua in 2004, initially with the goal of managing the local activities of the Pediatric Dengue Cohort Study (PDCS) conducted in partnership with UC–Berkeley and the Ministry of Health. The goal of the study, supported by the Pediatric Dengue Vaccine Initiative, is to characterize the transmission of dengue virus in a cohort of children in Managua. Recent data revealed unexpectedly high rates of dengue virus transmission—by age 10, 90%–95% of children in Managua have been infected with one or more of the four dengue virus serotypes, and up to one in four children is infected with dengue virus each year.[26] The study, which is currently in its fourth year, monitors a cohort of approximately 3700 children aged 2–12 years at high risk for dengue in Managua's densely populated, low- to mid-socioeconomic status District II near the Lago de Managua. Unique in Central America both in quality and magnitude, the project serves as the basis for

epidemiological and vaccine safety research and establishes the infrastructure for eventual testing of a safe tetravalent dengue vaccine with the potential to dramatically improve the fate of tens of millions of people around the world infected with the virus every year.

The PDCS takes place through collaboration among the Socrates Flores Vivas Health Center, the National Pediatric Reference Hospital Manuel de Jesús Rivera, the Virology Department at the CNDR, and SSI personnel working in informatics, quality control, and field operations within the community. The key personnel are SSI trainees and long-term collaborators. SSI's office in Managua administers the project, coordinates operations, performs the financial management, and executes the payroll of 25 employees and more than 100 contract workers, whereas SSI's San Francisco office guarantees financial transparency and fulfills the immediate needs of the project by procuring and shipping necessary supplies.

Because the PDCS is an international initiative, all the work performed must adhere to strict quality-control procedures, including GLP and GCP. To do so, all personnel and all participating institutions had to raise their standards of operations, and this exigency precipitated a new level of proficiency—in the clinic, field, and laboratory. This proficiency has improved the quality of the scientific endeavor tremendously, has caught the attention of the international scientific community, and has generated great pride in the project on part of the Nicaraguan study personnel and participants from the community.

Implementing Information Technologies: A Local Initiative

Once a year, a blood sample must be drawn from all 3700 PDCS participants. This requirement proved challenging during the first year of the study because of difficulty localizing clinical records rapidly, confusing home addresses (because of the lack of street addresses in Managua), and complicated fieldwork logistics. Furthermore, double data entry of all the information was an arduous process that took many personnel several weeks to perform.

As a local initiative to facilitate the annual sample collection process, SSI's Nicaraguan Informatics Director and study personnel explored options of ICT that could aid the project. SSI does not limit its technology transfer program only to technologies that can be deconstructed into simpler or cheaper versions but also over the years has implemented existing technologies that are affordable and appropriate to the circumstances. Thus, in this case, in direct response to the interest of our local collaborators and the requisites of the project, SSI once again aligned itself with the needs of its partners and supported the initiative.

As a result, in just a few months, SSI–Nicaragua catalyzed the implementation of a series of low-cost yet cutting-edge ICTs. Using readily available standardized hardware and software, our Nicaraguan informatics engineer programmed, designed, and supervised the implementation of a customized ICT system that includes GIS to map and easily locate study participants' homes, PDAs for paperless data entry and wireless data upload, barcode printing and scanning for tracking participant information and specimens, fingerprint scanning for facilitating patient identification and follow-up, low-cost communication systems (Skype, two-way radios), scanners for electronic backup of all documents, and computerized information systems with integrated databases for information management and control.[27] Although the systems were initially developed to facilitate the annual sample collection and home visits, they have now been applied in an integrated manner to other aspects of the study as well as to many other routine procedures in the Health Center and Virology Laboratory. They have not only greatly aided fieldwork but have also improved quality control at all levels far beyond the initial objectives and expectations.

During 3 years of operation, the team has found that the use of these technologies greatly streamlines information flow and accessibility, improves the quality of data and quality-control procedures, and reduces operational costs. Local personnel at many levels have received hands-on training and have not only quickly mastered the skills but also gained tremendous self-confidence in the process and now can train their peers in the use of the technologies. The implementation of the ICTs has not only facilitated PDCS operations but has also built critical information technology and other infrastructure in Nicaragua—the second-poorest country in the hemisphere—which will allow improvements in public health for years to come. Thus, we have witnessed the tremendous potential for using ICTs to bolster the public health infrastructure in resource-limited developing-country settings.

Improving Accessibility to Health Services with Technology

The increased availability of resources, the newfound abilities and confidence of the study personnel, and the knowledge gained have created a

platform for future projects with far greater effect on public health. Along with the scientific endeavor of the PDCS, there is a service commitment on the part of SSI and the Nicaraguan investigators and health workers to improve the health of their communities. During the last few years, a new initiative evolved from the highly successful implementation of low-cost ICTs during the PDCS. The positive effect of these technologies sparked our Nicaraguan collaborators and Ministry of Health officials to envision another project with far-reaching consequences in improving the local public health. This is an entirely local response to the urgent need to overhaul the vaccination and prenatal care system in Nicaragua and is tailored to help resident scientists and health care workers meet this need.

Nicaragua's public health system is currently struggling to meet the goal of the Pan American Health Organization for 95% vaccination coverage of preventable infectious diseases by 2008 as well as the Millennium Development Goal of a three-quarters reduction in the maternal mortality ratio by 2015.[28,29] Current efforts at providing vaccine coverage and prenatal care in Managua suffer tremendously from a lack of computerized registries and other inefficiencies. One major obstacle comes from the fact that the city of Managua operates without street names or addresses, resulting in the loss of much time spent locating homes, because directions are generally given relative to landmarks that may no longer exist. This confusing system is the result of the devastating 1972 earthquake, after which the city was rebuilt without urban planning, street signs, or house numbers. Also, the vaccination and maternal health system has chronic deficiencies including the use of manual data management; lack of a central location to safeguard all records; inaccessible and out-of-date data; discrepancies in the information on records (mostly addresses); incomplete census data of children; and the poor reporting system for newborns. Also, resources are often wasted by duplicating vaccinations because of lack of accessible records and the duplication of prenatal and postpartum health services in various locales.

This project, which is aimed at enhancing national immunization coverage of vaccine-preventable diseases and expanding prenatal care services, builds on the experience gained by Ministry of Health and local SSI personnel during the PDCS. The initial phase of the project is taking place at the Socrates Flores Vivas Health Center, which serves a population of approximately 62,500 and has been the base for the PDCS for 3 years. It will then be rolled out to a second health center with fewer resources, located in the semirural district of Ticuantepe and representative of the conditions of most health centers in Managua. Our ultimate goal after successful implementation of the pilot phase is to expand the initiative to the additional 19 health centers in Managua and then to the rest of the country.

The project will incorporate several technologies that will streamline information flow and accessibility, improve the quality of data as well as quality-control procedures, and reduce operational costs. A database of pregnant women and live births in each of Managua's 21 health centers is being created; a computer-based system of expectant mothers' prenatal visits and children's vaccination history is being implemented through the use of digital registries along with PDAs in the field and in the Health Center/health posts; unique identifiers will be provided to mothers and children to enable immediate access to files through the use of barcodes on vaccination cards; and children's homes will be georeferenced to facilitate field visits.

As a first step in this initiative, SSI's informatics team in collaboration with the Ministry of Health designed, refined, and implemented a new informatics tool, the Immunization System Database (SIPAI), to capture data during vaccination campaigns and routine immunizations and enable real-time analysis. In June 2007, the new database was launched, and 100% of the health centers in Managua adopted it after a training workshop conducted by SSI and the Ministry of Health. The implementation and use of the SIPAI database allows automation of immunization data, generates comprehensive vaccine coverage information, and facilitates immediate decision making that affects immunization indicators. The success of this initiative demonstrates the capability of SSI's informatics team to implement other IT solutions for further improvements to the vaccination and maternal health systems.

As with the PDCS, local personnel will be trained in the use of the technologies and applications and will be responsible for the implementation and quality control of the program. SSI–San Francisco will raise funds and will oversee the financial aspects, whereas the local office will administer the project. A great deal of interest and the potential for national expansion has already been expressed by high-level officials in the Nicaraguan Ministry of Health, who have committed to providing computers and subsequently wireless access to all health centers in Managua. Ensuring high levels of vaccination coverage in compliance with the WHO Expanded Program of Immunizations recommendations is a top priority for the Ministry of Health. Because of Nicaragua's high rates of maternal mortality, fertility, and adolescent pregnancy compared with those of other Latin American countries, medical care

for pregnant women is also one the principal priorities of the Ministry of Health, as demonstrated in the *Nicaraguan National Health Plan 2004–2015*. We expect that this new project will be fully implemented in the city of Managua and eventually the entire country of Nicaragua. Improved maternal care and an efficient immunization system, two health areas that often suffer in impoverished nations, should produce significant gains in survival rates of mothers, newborns, and children in Nicaragua.

Thus, we have shown that solid relationships built over 20 years of work in Nicaragua have empowered local researchers and have resulted in an exceptionally high quality of work, as exemplified by the PDCS. SSI is witnessing how local personnel now take leadership in solving their country's problems and involving the community at large.

Conclusion

In an age of vaccines, antibiotics, and dramatic scientific progress, infectious diseases that could have been brought under control continue to kill at an alarming rate in developing countries. Because the scale and complexity of the crisis is so great and the causes are linked so closely to poverty, the situation is often perceived as hopeless. However, on the bright side, efforts to prevent and control infectious diseases are among the most practical and achievable ways of alleviating poverty and furthering social and economic development. With appropriately trained personnel, resources, tools, and effective partnerships, low-cost interventions that lessen the burden of these diseases can be implemented. SSI's mission is to facilitate this process so that all nations can combat infectious diseases and reduce their effect locally.

SSI's overall mission has not changed since the AMB/ATT program was first conceived 20 years ago, but the means with which SSI achieves its goals have evolved over time. Training and technology transfer are critical elements in a long-term process that leads to the development of overall research and scientific capability of individuals, groups, institutions, cities, and eventually whole nations to detect and tackle relevant infectious diseases and other health issues affecting their communities.

Capacity building of human resources in a respectful and culturally appropriate manner is key to the success of SSI's strategy, and the resulting partnerships, collaborations, friendships, and trust engendered by the process have created a generation of young researchers and public health personnel in developing countries who have increased confidence, capability, and commitment to work of the highest quality. This empowerment has led to local researchers taking important initiatives, learning the language necessary to communicate relevant information to influence their leaders, creating lasting partnerships with researchers around the globe, and participating in international projects and collaborations. SSI is thrilled to be the catalyst of the change it has witnessed over time, where technology is just a starting point. SSI is honored to work with the people who embody this change and privileged to grow with them.

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Conflicts of Interest

The authors declare no conflicts of interest.

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