Strengthening Microbiologic Laboratory Systems
to Support Infectious Disease Prevention and Control Programs in Under-resourced Countries

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Introduction

On May 9-10, 2005, the American Society for Microbiology’s (ASM), Public and Scientific Affairs Board (PSAB) sponsored a meeting to discuss laboratory needs to support infectious disease prevention and control programs in under-resourced countries.

The meeting focused on:

1. the need to increase the awareness of the importance of laboratories to the success of public health programs in under-resourced countries

   and

2. ways to build on existing or planned programs that require a good laboratory system for a program’s success.

The laboratory system established for polio eradication and the growing requirements for laboratories as part of the President's Emergency Plan for AIDS Relief (PEPFAR) program were highlighted. The possibility of pairing laboratories from well-resourced countries with laboratories in under-resourced countries was also considered.

ASM is committed to furthering policies and programs which enhance the capacity of laboratories globally to strengthen detection and response to infectious diseases. Nowhere is this more challenging or more important than in under-resourced countries.

As major programs such as PEPFAR and the Global AIDS Program are assessed, the laboratory underpinning needed to assure the effectiveness of the programs must be a critical part of the evaluation. For example, for PEPFAR, steps must be taken to assure not only that HIV is diagnosed accurately, but also that accompanying infections such as tuberculosis, and bacterial diseases including pneumococcal infections can be adequately diagnosed. In addition in many countries, laboratories established for polio eradication may be willing to broaden their portfolio for diagnostic purposes; these laboratories have a superb track record, including those with few resources.

Measurement of health burden in under-resourced countries will require microbiologic assessment of infectious diseases. The Bill and Melinda Gates Foundation and the World Health Organization (WHO) have begun developing tools such as health metrics to assess morbidity and mortality in developing countries. Laboratory requirements can be fulfilled through a public, private or combined enterprise; the potential to utilize laboratories and faculty in academic settings to benefit public health programs was also put forward based on the thesis that universities are public trusts. Efforts to assure support by the ministry of health for the laboratory elements required for successful public health programs are also needed. ASM is committed to working with both governmental and non-governmental partners to strengthen the microbiology laboratory systems, vital to assuring the effectiveness of public health interventions for infectious diseases.
Background

Global Polio Laboratory Network

The Global Polio Laboratory Network (GPLN) was established to provide diagnostic capacity in the global fight to eradicate the disease. The network consists of three tiers of laboratories: National and sub-National, Regional Reference, and Global (Figure 1).

These three tiers work together to determine transmission patterns of wild polio virus, to identify trends and impact of wild polio virus, and to establish end points when elimination and eradication are achieved. ([http://www.afro.who.int/polio/lab.html](http://www.afro.who.int/polio/lab.html))

Figure 1: Structure of the Global Polio Laboratory Network (18)

Throughout the world there are 7 specialized reference laboratories, 15 regional reference laboratories, and 124 national and sub-national laboratories (Figure 2).
Laboratories are selected for inclusion in the GPLN based on several criteria. First the laboratory must be nominated by the government from existing laboratories. Secondly, WHO conducts an on-site visit to the laboratory to determine if the laboratory has suitable infrastructure and to assess the background, experience, and quality of staff; existing or potential expertise in technologies used by network; expected workload; and transportation and communication links. Finally, the laboratory must achieve an acceptable level of performance in proficiency testing before the laboratory is accepted into the GPLN.

The GPLN enrolled pre-existing laboratories and implemented polio diagnostic procedures. This caused many laboratories to drop other diagnostic activities while strengthening their ability to conduct polio diagnostic procedures.

Each WHO region has a Regional Laboratory Coordinator who is responsible for the on-going monitoring of laboratory performance (e.g., routine data, accreditation, proficiency tests), resource mobilization, coordination of training, procurement of supplies and equipment for network laboratories, assisting laboratories with problem solving, and coordination with surveillance and immunization personnel to use laboratory data for action.

Surveillance is conducted by acute flaccid paralysis (AFP) officers; there are more than 3000 staff that support surveillance efforts including approximately 1500 technical staff. In 2004, 25-50% of staff time was spent in support of non-polio activities including the tsunami relief efforts in 2004-2005.

The GPLN has learned many important lessons including:

- National governments may not provide the resources needed to support laboratory activities, even for high priority diseases.
- WHO has an important advocacy role for strengthening public health laboratories.
- The functionality of laboratories is not solely dependent on trained staff.
- Linking laboratory and field surveillance activities is important.
- High quality work depends on strong quality assurance programs including performance monitoring.

There is potential for the expansion of polio laboratories to include other activities, especially when expanded activities include similar technology platforms and use of data management and communication infrastructure. Additionally, there is interest in and expectation of GPLN to ensure the lasting legacy of polio eradication infrastructure. Yet, any additional activity must not jeopardize the polio eradication effort; additional resources must be obtained to cover additional activities and increased workload.

Polio eradication effort costs $50-75 million dollars per year; only 2-3% of this is allocated for the laboratory. How do we mainstream the effort used for polio eradication so others buy in once polio money goes away?

One complaint about the polio program has been the lack of communication and diagnostic capacity for non-polio related AFP. Both enterovirus 71 (EV71) and Japanese encephalitis (JE) may cause AFP. Through a partnership between pediatrics, the government, and the Universiti Malaysia Sarawak, surveillance and increased diagnostic capacity built upon the polio network has helped alleviate this complaint in Malaysia. Hand Foot and Mouth Disease (HFMD) typically presents as mild disease; occasionally infection may result in aseptic meningitis, flaccid paralysis, rarely encephalitis (typically from EV71). Major etiological agents for HFMD are coxsackievirus A16 (CA16) and EV71. The HFMD surveillance program in Sarawak began in March 1998 with outbreaks occurring every three years. The 2000 EV71 outbreak was centered around the Gawai Harvest Festival in February and persisted into May. Fatal outbreaks elsewhere in the region led to fear among the public and the recognition of non-EV71 associated syndromes in late 2000. The public health measures implemented in 2003 to combat SARS, limited the 2003 outbreak of HFMD.

Global Measles Laboratory Network

The Global Measles Laboratory Network (GMLN) was established in 2001 by the World Health Organization (WHO), United Nations Children's Fund (UNICEF), Centers for Disease Control and Prevention (CDC), and numerous experts worldwide (3). It was developed along the lines of the GPLN and utilizes much of the GPLN infrastructure. The GMLN’s two primary functions are to monitor and verify circulating virus strains and assist in determining the susceptibility profile of the population (9). During outbreaks the GMLN will confirm initial cases of measles and determine genotype of the circulating wild virus, contributing to the global genome mapping of measles. They may conduct seroprevalence studies to assist in evaluating the impact of vaccine campaigns and outbreak forecasting (9).
Although the polio laboratories utilize cell culture based procedures for polio diagnosis, many of these laboratories have the capability and capacity to perform serologic testing for measles. Given the overlapping infrastructure requirements that both diseases utilize, there was a belief that all polio laboratories would serve as diagnostic centers for measles. However, this was not always the case as many measles laboratories were set up in universities without links to the GPLN.

Through the Global vaccine preventable laboratory network, laboratory capacity for yellow-fever and rubella has also been implemented (Figure 3). The laboratories in Ghana and Cote d’Ivoire have provided diagnostic capacity for other West African counties. These laboratories will function as long as joint public and private partnership with government in country transcend politics and they are externally supported.

**Figure 3**: Global vaccine-preventable Laboratory Network, September 2004 (2, 5)

The strength of both the polio and measles model comes from the focus on accuracy, reporting, and action. Only the polio model has performance goals that are measured yearly.

**Global Outbreak and Response Network**

The Global Outbreak and Response Network (GOARN) was formed in 2000 by representatives of technical institutions, organizations and networks in global epidemic surveillance and response. The World Health Organization coordinates international outbreak response and provides a secretarial service for the network. Much of GOARN’s efforts related to laboratories focus on emergency response, and novel pathogens. Technical institutions, networks and organizations with the capacity to contribute to international outbreak alert and response form the partnership; members include
- scientific institutions in Member States,
- medical and surveillance initiatives,
- regional technical networks,
- networks of laboratories,
- United Nations organizations
- Red Cross
- international humanitarian non-governmental organizations.

SARS first tested the GOARN system. This network contributed to a multi-country field response which included 115 experts from 26 institutions in 17 countries, 13 laboratories in 9 countries, and more than 50 clinicians in 14 countries. A virtual network of epidemiologists was created and consisted of daily telephone conference calls between 11 institutions and 32 epidemiologists. Additionally, ten institutions participated in a SARS Modelling group.

In 2003 the GOARN steering committee concluded that the laboratory network that supports GOARN should:

- Include a wide range of infectious agents, flexible in terms of testing range
- Utilize the existing networks, e.g., influenza, polio, measles
- Be sustainable over periods of relative inactivity;
- Develop surge capacity to cope with additional workloads from the region in which it is situated;
- Provide technical assistance through cooperation between laboratories

Lessons learned by GOARN’s responses to SARS, the tsunami in January 2005, and Marburg are many:

- Both virtual and functional laboratory networks are needed to support outbreaks of international impact.
- Awareness of existing laboratory capacity and personnel worldwide preparedness and surge response is lacking.
- A platform for field evaluation of new technologies, treatments and vaccines is needed.
- Scientists and their administrators often insist upon protection of their scientific contribution by some legal venue. (e.g., Vietnam held up sending the H5N1 influenza strain to CDC until they were assured intellectual property rights.)

Today the network consists of 168 volunteer laboratories and 120 partners.

The six WHO regional offices with support from WHO headquarters will provide templates and guidelines that partners that allows them to share with others with assurance that their rights are protected. Additional guidelines will include:

- how to set up collaborative studies,
- best practice standards for laboratory management, data and specimen storage
- career enhancement opportunities.

Regional networks will help each other with site evaluations, protocol standardization, proficiency programs, and fostering relationships. WHO will provide access to training
programs for partners on such topics as data management, events management, surveillance, and biosafety.

WHO will encourage partner laboratories to work together on activities such as evaluating rapid diagnostic tests and linking research laboratories with appropriate field sites. By working together, partners will become familiar with each others’ strengths and capacity and will provide opportunities for working together.

GOARN faced several challenges following the tsunami response in January 2005 (e.g., water and food-borne disease outbreaks, antibiotic resistance, mass vaccination, and directly observed therapy (DOTS)). Scientists from several of the polio laboratories assisted in the tsunami response.

Additional challenges resulted from the Marburg epidemic in March 2005. These included logistics, infection control, laboratory diagnosis and safe burials.

Given the growing concerns regarding the re-emergence of SARS and emergence of highly pathogenic avian influenza, GOARN must address several questions, including:

- What laboratory capacity is needed?
- What is the need for external quality assessment, and how can the need be met?

Additionally with the pending eradication of polio, GOARN needs to plan for containment of polio stocks and determine what laboratory capacity should be retained.

In many circumstances, treatment and care of patients must be supported by laboratory capacity. Clinicians must be trained to use and understand diagnostic laboratory tests to support patient care when it is vital to assuring good clinical outcome.

If there is a specific need in a country, the MOH may support an extension of a disease-specific laboratory (e.g., polio). Laboratories used solely for outbreak investigations are unlikely to be sustainable. Also, if a laboratory becomes disease-specific or a research laboratory, the MOH may be less likely to support it.

**Integrated Capacity Development Program for Laboratory Specialists, WHO/Lyon**

Recognizing the gap between national epidemiology programs and public health laboratory diagnosis in many under-resourced countries, WHO established the Integrated Capacity Development Program for Laboratory Specialists in Lyon, France in order to:

- improve diagnostic capacity for infectious diseases
- encourage appropriate public health practices
- extend the network of national and international laboratories to ensure timely exchange of information;
- ensure the availability of rapid, effective and secure means of transportation for diagnostic materials and laboratory samples
- develop appropriate principles and practices for quality control.
Didactic training, case-studies integrating epidemiology and laboratory practice, computer and internet training, and laboratory practice are used to train participants over the course of two years. An integral part of this program is communication with participants while they are in their home country. The program fosters a long-term relationship with participants that continues beyond the end of the two years and aims to establish a surveillance network (16).

Potential participants must hold a senior technical or management position in a national referral laboratory of the Ministry of Health (MOH), have a university degree in microbiology or another biological science, and have excellent knowledge of French or English language. Potential participants must be nominated by their governments and are screened by WHO officers during country visits (16).

Between 2001-2004, the program has trained three groups. The first was from Africa, the second was from the Middle East, and the third was from the newly independent states. Participants came from the following countries: Central African Republic, the Democratic Republic of the Congo, the Islamic Federal Republic of the Comoros, the Republic of Cape Verde, the Republic of Chad, the Republic of Equatorial Guinea, the Republic of the Congo, the Hasemite Kingdom of Jordan, the Islamic Republic of Iran, the Lebanese Republic, the Republic of Iraq, the Republic of Sudan, the Republic of Yemen, the Syrian Arab Republic, Georgia, the Republic of Belarus, the Republic of Bulgaria, the Republic of Moldova, the Republic of Turkey, Romania, the Russian Federation and Ukraine (16).

This program enabled participating laboratories to expand their diagnostic capacity to cover polio, measles, yellow fever, meningitis, rubella, and cholera.

Integrated Capacity Development Program for Laboratory Specialists in Lyon did not realize its full potential due to three major reasons:

- lack of sustained funding
- human resources
- lack of ability to pair laboratories in developing countries with reference, research, public health organizations, or university laboratories

The lack of sustained mid and long-term funding for laboratories in under-resourced countries has been problematic. The MOHs have frequently not supported the laboratories once capacity has been established.

Participants were trained to perform assessments of laboratories, hospitals, epidemiology, public health, and MOH which would result in written reports. However, many participants never performed the assessments due to lack of funding.

Although communication continued with participants once they returned to their home country, the laboratories were not paired with laboratories from developed countries.
The most appropriate person was not always selected for participation in the program. The MOH hand-picked the participant from within the government; sometimes this person was not appropriate. There may be a need to identify participants from private organizations or universities with good links to government who can get things done.

Political will, passion, and funding are needed to sustain laboratory capacity.

President's Emergency Plan for AIDS Relief and Global AIDS Program

Global AIDS Program (GAP)

One of the US government’s global health programs is the Global AIDS Program (GAP). The mission of GAP is to assist under-resourced countries prevent HIV infection, improve treatment, care, and support for HIV infected people, and to build capacity to address the global HIV/AIDS pandemic. Through partnerships with governments, communities, and national and international institutions, CDC staff are implementing GAP programs in many under-resourced countries to accomplish this mission.

There are 25 country based programs (Figure 4) and four regionally based GAP offices which include the Asian Regional Program, the Caribbean Regional Office, the Central American Regional Program, and the Southern Africa Regional Program. Together the country based and regional program serves 52 countries (8).

Figure 4: GAP Country Based Programs (6)

The major GAP activities include prevention, care and treatment, and surveillance and infrastructure development.

GAP’s HIV prevention programs focus on behavior change, voluntary counseling and testing, prevention and treatment of other sexually transmitted infections, and prevention of medically acquired HIV. GAP’s HIV/AIDS treatment and care programs include prevention and care of
opportunistic infections including tuberculosis, prevention of mother-to-child HIV transmission, and operational research related to developing program models, standards and guidelines. GAP’s surveillance and infrastructure development program focuses on laboratory capacity building, surveillance, monitoring and evaluation, operational research, informatics, training. (8)

President's Emergency Plan for AIDS Relief (PEPFAR)

In January 2003, President Bush made a commitment to substantially increase US support to addressing the global HIV/AIDS epidemic by allocating $15 billion over 5 years to a global initiative to combat the HIV/AIDS epidemic, President's Emergency Plan for AIDS Relief (PEPFAR) (1, 4). Fifty-five percent of the money is for the treatment of individuals with HIV/AIDS (Seventy-five percent of this allocation will be spent on the purchase and distribution of antiretroviral drugs in 2006 through 2008). The remaining 45% will cover palliative care (15%), HIV/AIDS prevention (20%), and help for orphans and vulnerable children (10%) (14).

Currently PEPFAR provides funds to 15 target countries: Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Zambia, and Vietnam (14). The PEPFAR program is currently being reviewed by the Institute of Medicine, with Jaime Sepulveda as chair of the committee.

All GAP programs depend on capacity-building and infrastructure-strengthening to accomplish their goals. In order to build laboratory capacity, minimal standards must be met prior to filling high-end requests. Laboratory service must have an impact at the point of care and must be timely and responsive to epidemics. The laboratory system must be able to support expanded national programs. However, there are major challenges to implementing this mandate. Ministries of public health must use their available laboratory resources, if any, for a broad range of prevention and control programs. Laboratory services supported by GAP must build on available laboratory services, if any. In any case, laboratory services must be assured to diagnose HIV infection as well as to diagnose infections in HIV-infected individuals, including tuberculosis, and invasive bacterial infections.

Fundamental questions must be answered prior to increasing laboratory capacity. They include the following questions:

- What is the current laboratory capability and capacity?
- What drives the need for renovation of laboratory facilities and construction?
- What drives the scope of training needs?
- What drives the need for development of new purchasing/contract mechanisms or modification of existing ones?
- What is the current laboratory infrastructure?
- What are the existing laboratory facilities?
- Where are the existing laboratory facilities?
- What mechanisms for training staff, hiring new staff, managing, and monitoring performance are in place?
- What is the relationship of ancillary services, e.g. central medical stores to the laboratory?
- What is the organizational structure of the laboratory within the MOH?
Common findings from these questions indicate that there are a wide range of competencies indicating a need for quality standards. Additionally, there is a need to improve training opportunities for critical laboratory staff, including laboratory management training. The loss and sub-optimal distribution of trained personnel must also be addressed. Biosafety in the laboratory must be assured. Fears that additional work-load may overwhelm a weak laboratory system must also be addressed.

As a result of the magnitude of the pandemic and the response by large numbers of agencies and organizations involved domestically and internationally, complex, multi-agency, multi-level partnerships and collaborations have been established. Communication between these organizations and within partnerships has proved to be a challenge.

Therefore a stepwise approach is needed. The MOH and partners must develop a country plan for strengthening laboratory infrastructure based on measurable objectives. A working group should be created which will identify action steps, assign responsibility, set realistic goals in specified time, and convene regularly to monitor progress. This working group should consist of the highest level officials in MOH, in-country HIV/AIDS program and laboratory leaders, and multilateral partners. The country plan to strengthen laboratory infrastructure must addresses 3-5 major objectives (e.g., provide services to meet the need to screen 1 million persons in the next year). These objectives must be measurable and meet the quality assurance standards. Quality Assurance as defined by the International Organization for Standardization is “Planned and systematic activities to provide adequate confidence that requirements for quality will be met” (ISO 8042, 3.4; NCCLS).

Resources are available to assist in building laboratory capacity. There are many technical experts from the Association of Public Health Laboratories (APHL) and universities as well as bilateral donors that are willing to assist in this effort. CDC is also exploring collaborations with ASM for technical assistance. Technical guidance documents have been developed and reports have been generated to describe how to implement laboratory systems.

In summary, laboratory capacity is a multi-dimensional challenge that will need to be addressed to have a successful GAP program. We must be assured that all persons under treatment have been diagnosed accurately, and that the laboratory system needed to assure effective treatment is functioning adequately. Laboratory systems must be tested to assure quality. Laboratory models are available and they should be utilized in development of laboratory systems in GAP countries. More consideration should be given to how the clinical laboratories set up for diagnosis and monitoring treatment of persons with HIV can be linked with other networks and public health laboratories to enhance surveillance.

**Private Partners**

Universities may have a major role to play in enhancing the strength of laboratory systems in a country to support public health. For example, the Universiti Malaysia Sarawak has the laboratory capacity to test for flaviviruses, enteroviruses, and adenoviruses. They also have the ability to conduct viral isolation, PCR, RT PCR on primary specimens, IgM serology, and
genotyping. There is a general feeling at the university that the polio program does not provide feedback to the clinician if a patient is diagnosed with non-polio acute flaccid paralysis. Both Japanese encephalitis virus (JEV) and Hand Foot and Mouth Disease (HFMD) may cause acute flaccid paralysis. Partnerships between pediatrics, government and this university allow for a strong surveillance network. The university conducts passive (hospital based) and active surveillance, including the laboratory assays necessary to determine the causative agent of AFP. Their active surveillance program includes reporting from sentinel clinics and primary health care settings. By recording and understanding trends, they are able to predict outbreaks. This information allows for the implementation of early public health intervention measures to curb an outbreak. The public health measures used to control SARS actually helped control HFMD EV71 outbreak because people used these measures at the beginning of the HFMD outbreak. The university leverages funding from a laboratory in Australia for much of its work. They have also received a grant from the Welcome Trust to extend surveillance to other resource poor-countries.

Another example of the vital role private institutions can play was evidenced by a surveillance project in India. In 1984 in the North Arcot district of southern India, Christian Medical College, Vellore established a vaccine-preventable disease surveillance system as part of a project to control polio. All private and government healthcare institutions were recruited for participation in the surveillance of AFP and also measles, pertussis, diphtheria, tetanus neonatorum and tetanus, rabies, encephalitis, meningitis, and hepatitis. Participating healthcare institutions were requested to complete a printed, self-addressed, postage-paid postcard when a disease was diagnosed. Laboratory confirmation was not required for reporting, and, in fact, all 5 microbiology laboratories in the area were private. Several important findings were identified as a result of this surveillance system. One-half of vaccine preventable diseases identified from rural areas and 99% from urban areas were reported from private institutions. It is essential for the government and private institutions to collaborate on surveillance issues; otherwise, the true burden of disease will remain unknown. Outbreaks of measles and pertussis were recognized early and public health measures were utilized to contain the outbreaks. Laboratory confirmation was obtained only when there was a specific need such as confirming polio or determining the cause of an outbreak of suspected anthrax in animals and humans. Without the participation of the laboratory none of the cases would have been confirmed, and the problems with clinical diagnosis of many of these diseases are widely acknowledged (11). Moreover, data from the laboratory could be serially monitored, thus identifying the introduction and increase of incidence/prevalence of malaria and HIV infection in the district. This surveillance system supported by laboratory service has subsequently enabled the introduction of investigations into the incidence of Hib meningitis, as a forerunner to a vaccine probe study that is soon to be started.

This surveillance model was transplanted in another district, now with the government district health office acting as the nodal agency (coordinating point), so that it would become widely replicable and sustainable in the long term. Here, the importance of the laboratory confirmation was immediately visible by the ability to document that leptospirosis was an important public health problem that had previously been ignored or denied. When cholera appeared in the district it was promptly detected, diagnosed and intensive control measures instituted. A large outbreak of food poisoning was pinpointed to a specific source of water. The fact that clinicians
contributions to the surveillance system resulted in public health action served as a huge motivation factor. A retrospective analysis of reporting of vaccine preventable diseases prior to 1984 indicated that most rural healthcare institutions were not reporting any cases (11). Regular feedback in the form of a monthly bulletin was another reinforcement of motivation. Without government participation and leadership, this system will not be sustainable. An effort to expand this program with full government support is underway (10).

**Role of Foundations**

Foundations have a history of contributing to disease control and public health. In 1915, the Rockefeller Foundation funded a 30-year, effort to eradicate yellow fever. Physicians and scientists set up laboratories and investigated the causes of the disease in South America and West Africa. The first yellow fever vaccine was developed by Sawyer in 1931 working in the laboratory at the Rockefeller Institute. In 1937, Max Theiler subsequently developed yellow fever viral strain 17D, a safer attenuated yellow fever virus, which allowed for a vaccine program to be developed. The first field trials were held in Brazil in 1938. (11) In order to produce enough yellow fever vaccine to meet demand, the Rockefeller Foundation established a vaccine production company in Brazil and Columbia.

Rockefeller established an arboviral laboratory 1954 in Brazil and Columbia. This laboratory contributed to the training of scientists and laboratorians, increased diagnosis and capacity. Eventually, the government of Brazil began supporting this laboratory. Walter Reed invested next in PAHO and collaborations with the University of Texas medical branch. Fifty years later, the efforts begun by the Rockefeller Foundation are still having an impact on influenza, viral hepatitis, rotavirus, herpes, and HIV. Sustainability cannot be achieved without 5-10 years of external support followed by institutionalization by the government.

Today, many foundations require the projects that they fund to have measurable outcomes. Increasing laboratory capacity may allow for measurable outcomes to be obtained. For example, one measurable outcome for HIV/AIDS may be number of opportunistic infections is decreasing because the number of people receiving ART is increasing. Without the ability to diagnose opportunistic infections, we cannot determine whether or not ART is improving the health outcomes of individuals taking ART.

To improve global health, the Bill and Melinda Gates Foundation is pushing for a more accurate assessment of the global health burden of disease, and tools to more accurately measure that burden. Towards that end, the Gates Foundation has given $50 million dollars over seven years to assist with the WHO’s Health Metrics Network (HMN). Additional funding for this initiative has been provided by Department for International Development (U.K.), U.S. Agency for International Development, and the Danish International Development Agency (17).

The goal of HMN is to increase the use and availability of health information globally through investments in health information systems with agreed upon standards (15).

The Gates Foundation understands the importance of laboratory capacity and, although not currently funding laboratories, they will and do advocate for increasing laboratory capacity in
under-resourced countries. They are willing to assist in bringing together the private sector to help fund Public Health Institutes.

Other foundations, such as the Ellison Medical Foundation, are interested in increasing laboratory capacity by supporting training programs. The Ellison Medical Foundation provided resources through the CDC Foundation to implement a regional Field Epidemiology and Laboratory Training Program (FELTP) in Kenya. The goal of the FELTP is to strengthen the epidemiologic and laboratory services of the Kenya Ministry of Health and the East African Region. The program trains both field epidemiologists and laboratorians in the fundamentals of each discipline. Biosafety, laboratory practices, and epidemiologic competencies will be taught over a two-year period (7). Some donor money is allocated for the operationalization of country budget priority (planning process); it is not earmarked for specific projects.

The Harvard School of Public Health received $1.1 million dollars from the Ellison Medical Foundation in 2002 to offer training in global infectious diseases to scientists from both the United States and from disease endemic countries. This training will focus not only on microbial pathogenesis and microbial evolution but also on the development and application of new vaccines and drugs. Partner institutions include the Centre for Health and Population Research in Bangladesh; Mahidol University, Faculty of Tropical Medicine in Thailand; National Institute of Cholera and Enteric Diseases in India; and Cheikh Anta Diop University in Senegal. In addition to training a cadre of scientists in global infectious diseases, this effort seeks to create sustainable research programs at several major universities in disease-endemic countries (12).

In 1988, the Rockefeller Foundation funded the International Clinical Epidemiology Network Trust (INCL, a non-for-profit organization made up of a global network of clinical epidemiologists, biostatisticians, social scientists, and other health care professionals (10). The goals of INCLEN include strengthening national health care systems and improving health practices globally. By providing professionals with the knowledge and skills to analyze the efficacy, efficiency, and equity of interventions and preventive measures, INCLEN hopes to achieve these goals. The four specific core strategies outlined in INCLEN’s 2003-2007 Strategic Plan are

1. Strengthen INCLEN's goal of regional and national research and capacity building functions;
2. Achieve financial sustainability for INCLEN's infrastructure;
3. Sustain and create new programs in high priority health problems in developing countries;
4. Create new programs in leadership and management and clinical epidemiology through a Virtual Campus. (10)

Consideration should be given to linking the surveillance networks within INCLEN to microbiologic laboratories to focus on public health issues.
Recommendations (Note: These recommendations are not listed in priority order.)

1. Improve the understanding and knowledge of those developing, implementing and evaluating PEPFAR and GAP as to the critical need for adequate laboratory systems to support the goals of those programs, both for diagnosis of HIV infections and for clinical management of patients. This includes those directly involved in the program and those evaluating the program at the Institute of Medicine. Accurate laboratory diagnosis assures that non-HIV-infected persons are not treated with anti-retroviral therapy; in addition, laboratory diagnosis of STIs is important for HIV prevention programs. Diagnostic tests for infections such as tuberculosis and invasive bacterial infections are critical for treatment of HIV-infected persons; in addition, diagnosis and treatment of tuberculosis will prevent further spread. In evaluating PEPFAR programs, the degree of reduction in associated infections may be one of the best indicators of the success of the program, but laboratories are needed to have this evaluation tool available.

2. More consideration should be given to linking the clinical laboratories established with funding from PEPFAR and GAP for diagnosis and monitoring treatment of persons with HIV to other laboratories to enhance public health surveillance.

3. Encourage polio laboratories to actively seek to address needs of highest priority in countries where additional resources could be leveraged to accomplish needed goals. Document successes of polio laboratories in supporting prevention and control programs of other selected infectious diseases. Polio laboratories should expand scope to encompass infectious diseases requiring strengthened laboratory capacity for prevention and control programs. Sustainable resources are needed to assure that existing resources of polio laboratories captured and refined to meet current needs as the polio program permits.

4. Assure recognition of the need for laboratory systems in under-resourced countries if the global challenge of assessing burden of disease with health metrics is to succeed. Assure that efforts at both the Harvard School of Public Health and at the World Health Organization are informed as to the need to assure an adequate laboratory system to support the diagnostic requirement to achieve a health metrics goal of assessing burden of disease. A major criticism of the Global Burden of Disease report has been the lack of accurate infectious disease data in under-resourced countries. In addition, recent emphasis on syndromic surveillance has demonstrated the need for laboratory confirmation.

5. Assure that those leading the effort (sponsored by the Bill and Melinda Gates Foundation) to establish science academies as advisers to ministries of health, recognize the critical role of adequate laboratory systems in support of the goals of prevention and control programs for infectious diseases. National Institutes of Public Health are being created with the goal to have core public health expertise to serve as resource to leaders. The National Public Health Institute (KTL) of Finland is working with WHO to create a global network of public health expertise.
6. Consider a Secretariat based in Geneva, possibly under the auspices of the International Union of Microbiological Societies, so that laboratories would have a global focus to address critical issues in their profession in support of public health goals. The Secretariat would work with WHO to link the various surveillance networks together (in collaboration with GOARN), to ensure that WHO's surveillance standards are met. *Other health professions, including medicine and nursing have such world organizations to forward public health goals (i.e., the World Medical Association, the International Council of Nurses, International Pharmaceutical Federation). Many countries have a Chief Nursing Officer and a Chief Medical Officer. Consider establishing a Chief Laboratory Officer.*

7. Enhance the understanding of public health policy leaders as to the importance of public health laboratories. At times, laboratory capacity has been confused with availability of reagents or training of personnel; a laboratory system encompasses far more (e.g., proficiency testing, information management, biosafety).

8. Increase awareness that biosafety and biosafety training must be incorporated into laboratory systems design, and is a prerequisite to biosecurity.

9. Increase awareness that universities and other private organizations may play a pivotal role in assuring needed laboratory expertise.

10. Assist with efforts to have existing well-developed programs and experienced persons partner with those in less developed programs in under-resourced countries to improve the capacity of laboratories to support public health goals.
Supplement to Recommendation 5.

The **International Union of Microbiological Societies** (IUMS) is an international organization comprised of three divisions, Bacteriology & Applied Microbiology (BAM), Mycology and Virology and by six specialist international committees, eight international commissions and two international federations. The goals of IUMS are to promote the study of microbiological sciences, to ensure that discussion resulting from international conferences, symposia and meetings are disseminated, to represent microbiological sciences in the International Council for Science (ICSU), and to foster and maintain relationships with other international organizations. [http://www.iums.org/AboutUs.htm](http://www.iums.org/AboutUs.htm)

The **World Medical Association** (WMA), an international organization representing physicians, was created to ensure the independence of physicians and to work for the highest possible ethical standards and care by physicians. Membership and funding is from approximately 80 National Medical Associations. [http://www.wma.net/e/about/index.htm](http://www.wma.net/e/about/index.htm)

The **International Council of Nurses** (ICN) is an international organization comprised of national nursing organizations. The ICN seeks to bring nursing together worldwide, to advance nurses and nursing practices worldwide, and to influence health policy. Through partnerships and alliances with governmental and non-governmental agencies, foundations, regional groups, national associations, and individuals, ICN is able to advance nursing through policies and professional practice. [http://www.icn.ch/abouticn.htm](http://www.icn.ch/abouticn.htm)

The **International Pharmaceutical Federation** (FIP) is a world-wide federation of national professional and scientific pharmaceutical associations that seek to obtain and assure health for all. FIP represents and serves more a million pharmacists and pharmaceutical scientists globally. [http://www.fip.org/](http://www.fip.org/)
References


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Meeting on Laboratory Capacity in Under-Resourced Countries
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May 9 and 10, 2005
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Meeting on Laboratory Capacity in Under-Resourced Countries
May 9 and 10, 2005
ASM Headquarters
Agenda

Monday, May 9, 2005

3:30 - 4:00 pm Refreshments/Break
4:00 – 6:00 pm Welcome/Introductions
   Review Agenda/Purpose of Meeting
   Overview of WHO Global Network (Chu)
   Polio/Measles Network; Integrated Disease Surveillance (Heymann)
7:00 pm Dinner: Tabard Inn, 1739 N Street, NW

Tuesday, May 10, 2005

8:00 - 9:00 am Breakfast
9:00 – 11:00 am PEPFAR (Martin)
   Field Epidemiology Training Programs (Field Epidemiology Laboratory Training Programs); International Emerging Infections Programs;
   USAID efforts; GEIS (DOD); Other efforts: regional networks
12:00 pm Working Lunch
11:00 am – 3:00 pm Discussion
   1) Are laboratories viewed as fundamental to healthcare and public health in under-resourced countries by world leaders? How do we gain increased visibility/attention/support/commitment by world leaders?
   2) What models could we put forward which might leverage current or planned resources for disease prevention and treatment? What are the building blocks?
   3) Is there a career path or other program for trained laboratorians from developed countries to establish laboratories in under-resourced countries? Is this part of a global health corps?
   4) Next steps
3:00 pm Adjourn
Appendix C: Global Laboratory Network for GOARN

**Field operations 2000-2005**
Afghanistan, Algeria, Bangladesh, Burkina Faso, Cambodia, Chad, China, Côte d’Ivoire, Democratic Republic of Congo, Ethiopia, Gabon, Guinea, Hong Kong, SAR, Indonesia, Kosovo, Laos, Liberia, Former Yugoslav Republic of Macedonia, Madagascar, Philippines, Republic of Congo, Saudi Arabia, Senegal, Sierra Leone, Singapore, Sri Lanka, Sudan, Thailand, United States, Vietnam, Zimbabwe

**SARS - coordination and communications through networks**
- GOARN: multi-country field response
  - 50 experts from 26 institutions in 17 countries
- Virtual network for SARS virology
  - 13 laboratories in 5 countries
- Virtual network for SARS virology
  - 31 experts in 25 countries
- Virtual network of epidemiologists
  - 32 epidemiologists, 11 institutions, daily telephonic conference
- SARS: Modelling network
  - 18 institutions

**THE LABORATORY NETWORK**
(GOARN Steering Committee, December 2003)
The laboratory network should be:
- Flexible in terms of testing range - that is, a wide range of infectious agents;
- It should utilise the current networks - influenza, polio, etc;
- It must be sustainable over periods of relative inactivity;
- It should have a capacity to cope with additional workloads from the region in which it is situated;
- There must be technical co-operation between labs.

**Lessons learned from laboratory response to SARS, HPI (Tsunami and Marburg)**
Recognize the need for having both virtual and functional laboratory networks to support outbreaks of international impact.
Lack of full awareness of existing laboratory capacity and personnel worldwide – preparedness and surge response.
Need to provide platform for field evaluation of new technologies, treatments and vaccines.
Recognize that laboratories and scientists must have some legal venue to protect their contribution.
The challenges we face (a short list):

Tsunami response (Jan 2005): Water and foodborne outbreaks, antibiotic resistance, mass vaccination, DOTS

Marburg response (March 2005): Logistics, infection control, laboratory diagnosis and safe burials

Re-emergence of SARS (???): what can be done for early detection? Rapid mobilization? Reagents, EQA?

Highly pathogenic avian influenza (When?): how to prepare for it? Lab capacity? Reliability of tests?

Eradication of polio (When?): plans for containment of stocks? What laboratory capacity should be kept?
Appendix C: Polio Eradication

Polio Eradication: global surveillance of Acute Flaccid Paralysis

Surveillance of acute flaccid paralysis: global laboratory network

Surveillance of acute flaccid paralysis: AFP surveillance officers

Criteria for selecting laboratories, global network for AFP surveillance

Regional Laboratory Coordinators

Mechanisms for Strengthening Polio Laboratories in Network
Monitoring performance: global AFP surveillance

- Targets for AFP reporting:
  - > 1 report ≤ 15 years of age per 100,000
- Targets for sample handling and lab performance e.g.:
  - > 80% samples collected within 14 days of onset and in lab within 3 days of collection
  - > 90% stool in PTF test
  - > 80% of results reported in 20 days
- Weekly reporting of data (core report) and publication of data in regional bulletin
- Annual proficiency test
- Annual accreditation (no site visit; attend a workshop with established performance criteria or accreditation)

May 2005

World Health Organization

Non-polio AFP Rate: 2004/2005 comparison

April 2004 – March 2005

World Health Organization

Stool Collection Rate: 2004/2005 comparison

April 2003 – March 2004

World Health Organization

Virus linked to common ancestor, West and Central Africa

World Health Organization

Lessons learned in polio laboratory network

- Important to link laboratory and field surveillance activities
- Strong, quality assurance programmes and ongoing monitoring of performance are key to high-quality work
- Staff training, even one, will not achieve functional laboratories
  - Loss of trained staff can lead to collapse of services
  - Extra supplements occasionally warranted to counteract high staff turnover in a goal-oriented, time-limited, programme
- Resource needs may not be available through national governments, even for high-priority diseases
- WHO has important advocacy role for strengthening public health laboratories

May 2005

World Health Organization

Potential for expansion of polio laboratories to include other activities

- Yes, especially, but not limited to, laboratory investigations using similar technologies (e.g., influenza, arbovirosis)
- Use of data management and communication infrastructure – with cost sharing
- Interest and expectation of polio laboratory staff to ensure a lasting “legacy” of polio eradication
- Resource needs must be met for any additional activities. Increased workload must not jeopardize support to polio eradication

May 2005

World Health Organization
Appendix C: Global Health Challenges

Global Health Challenges: The Critical Role for Laboratories

International Outbreak Response

CDC Futures Initiative

- Global Health. CDC will establish clear priorities for its global programs and increase global connectivity to ensure rapid detection and response to emerging health threats.

U.S. Returns on Global Investment

Global health issues have global consequences that not only affect the people of developing nations but also directly affect the interests of American citizens:

- Programs to control the spread of infectious diseases reduce the threat of epidemics that could directly affect U.S. citizens.
- Stable populations reduce pressures on economies and the environment and reduce the risk of humanitarian crises.

Source: USAID

U.S. Returns on Global Investment

- Healthy, productive citizens are essential for global economic growth and regional security.
- New technologies developed through research have direct application in the U.S. health system.

Source: USAID
CDC Global AIDS Program Mission

- GAP helps resource-constrained countries:
  - prevent HIV infection
  - improve treatment, care, and support for people living with HIV
  - build capacity/infrastructure to address the global HIV/AIDS pandemic
- GAP provides its assistance directly through CDC staff and through partnerships with governments, communities, and national and international institutions

Major GAP Activities

- HIV Prevention Programs
  - Including behavior change (abstinence, delay, risk reduction), voluntary counseling and testing, prevent/treat other sexually transmitted infections, prevent mother-to-child transmission, blood safety
- HIV/AIDS Treatment and Care Programs
  - Including diagnosis, prophylaxis and treating opportunistic infections, tuberculosis and HIV/AIDS, and operational research related to developing program models, standards and guidelines
- Program Infrastructure
  - Including surveillance, operational research, informatics, training, laboratory support and monitoring and evaluation

CDC GAP Program Model

- Surveillance
- Primary Prevention
- Care and Treatment

Laboratory Mandate

- Minimal standards are met before high-end requests are filled
- Service has impact at point-of-care
- Service is timely and responds to the epidemic
- Laboratory systems infrastructure sufficient to support expanded national programs

Major challenge to implementing the mandate

Balance between:

- Supporting direct quality technical laboratory services for HIV/STI/TB/OI
- Supporting the creation/strengthening of PH laboratory systems to support quality testing
National Approach

- Ministry of Health the principal GAP partner
- Direct support to GAP programs
e.g. Quality lab support to surveillance
  - Method development and review
  - Training, program implementation, and External Quality Assessment
- Building/rebuilding national/local laboratory systems (planning, construction, equipment procurement, training)

Fundamental Questions

- What is the current laboratory capability and capacity?
  - Drivers need for renovation of laboratory facilities and construction
  - Drives scope of training needs
  - Drives need for development of new purchasing/contract mechanisms or modification of existing ones

Common Findings

- Wide range of competencies
- Loss, sub-optimal distribution of trained personnel
- Need for quality standards
- Need for improved training opportunities for critical lab staff including laboratory management training
- Intermittent supply of reagents
- Congested and in some cases unsafe laboratory environment
- Fear that additional workload overwhelms weak laboratory system

Fundamental Questions

- What is the current laboratory infrastructure?
  - Laboratory facilities
  - Mechanisms for training staff, hiring new staff, managing, and monitoring performance
  - Relationship of ancillary services, e.g., central medical stores
  - Organizational structure

Stepwise Approach

Develop a country plan for strengthening laboratory infrastructure based on measurable objectives
- Create a working group that will agree on action steps, call and will assign (and accept) responsibility, set reachable goals in specified time, and execute regularly to monitor progress
  - Highest level officials in MoH, in-country HIV/AIDS program and laboratory leaders, and multilateral partners
- What: Develop a plan that addresses 3-5 major objectives (e.g., provide services to meet the need to screen 1 million persons in the next year)
Quality Assurance

“Planned and systematic activities to provide adequate confidence that requirements for quality will be met” (ISO 8042, 3.4; NCCLS)

Available Resources

- Laboratory team
  - Steering committee
    - policy and management
  - Primary country liaisons
    - manage the execution of the laboratory plan
  - Country team members
    - execute the country plan and provide critical linkage to the realities on the ground

- Laboratory Team (continued)
  - APHL and University partners
    - wide range of competencies, e.g., technical experts, assistance with staffing, procurement of reagents, equipment and supplies, experience operating routine laboratory services
  - Other bilateral donors
    - could take on any of the above roles and also active at times with policy development and other major facility construction and purchases

Available Resources

- Technical guidance documents, e.g., Evaluation of Rapid HIV Tests

- Reports and documents describing how to implement laboratory systems and how to carry out discrete steps in a testing process, e.g., collecting blood samples, biosafety, writing a procedure manual

Workshops for Standardization of Laboratory Methods for Diagnosis of Bacterial Meningitis
Protocols and Guidelines Serve as the Foundation for Processes & Procedures

CDC and WHO-AFRO led development of Guidelines for Appropriate Evaluation of HIV Testing Technologies

NEW
Guidelines for Quality Assurance of Rapid HIV Testing
May 4-6, 2004
2nd WHO-AFRO Laboratory Conference

International References

Available Resources

- GAP Laboratory Resource Documents being developed by laboratory team addressing each technical testing area
  - Audience: Country care teams and laboratory team partners, country directors
  - Topics Areas: HIV testing, CD4 testing, Hematology and Chemistry, HIV Molecular Diagnostics, Testing for opportunistic infections
  - Format: Concise, Critical elements for implementing a testing service
  - Availability: Currently available

Available Resources

- Training materials and curricula
  - Quality systems
  - Laboratory management (APHL)
  - HIV Rapid Test Training
  - CD4
  - Chemistry and hematology (working with the American Society for Clinical Pathology)

- Training delivery-up to now done by laboratory team, seeking partners for expansion phase

President’s Emergency Plan for AIDS Relief

- Prevent 7 million new infections (60 percent of the projected new infections) Large-scale prevention efforts, including voluntary testing and counseling, the availability of treatment will enhance prevention efforts by providing an incentive for individuals to be tested.
- Treat 2 million HIV-infected people First global effort to provide advanced antiretroviral treatment on a large scale in the poorest, most affected countries.
- Care for 10 million HIV-infected individuals and AIDS orphans Range of care, including support for AIDS orphans

Goals of the Initiative

- Increase preventive treatment and care for pregnant women and their infants
- Improve health care delivery systems in Africa and the Caribbean
Designated Countries

Africa
1. Botswana
2. Côte d’Ivoire
3. Ethiopia
4. Kenya
5. Mozambique
6. Namibia
7. Nigeria
8. Rwanda

Caribbean
9. South Africa
10. Tanzania
11. Uganda
12. Zambia
13. Vietnam

14. Guyana
15. Haiti

and Regional efforts through CAREC (Trinidad)

Summary

- Building laboratory systems is a multiple dimension challenge
- Laboratory program activities in some countries can serve as models
- Successful laboratory testing programs in industrial countries were not established overnight and they will not be in GAP countries...but if treated as an emergency, road maps are available to expedite the work!

Aconcagua – 23,000 ft
The emergence of human enterovirus 71 in the Asia Pacific Region

M. Jane Cardosa
Universiti Malaysia Sarawak
April 2005
Many pathogens normally circulate in one place at one time

**EXAMPLE:**
CNS DISEASE IN SARAWAK

**METHODS**
- Flaviviruses - Dengue & JEV
- Enteroviruses - non-polio EVs
- Adenoviruses - Species B & C
- Virus isolation
- PCR, RT PCR on primary specimens
- IgM serology

**CNS DISEASE IN SARAWAK**
1998-1999
(passive; hospital based)

**THE STORY OF MISDIAGNOSIS OF AN ENCEPHALITIS OUTBREAK AMONG PIG FARMERS**
A JEV OUTBREAK IN SARAWAK
Coincided with the outbreak of fatal Nipah encephalitis in Peninsular Malaysia

ACTIVE SURVEILLANCE
- Sentinel clinics
- Primary health care settings
- Example of HFMD
  - Major etiological agents: CA16, EV71
  - Mild disease mostly, occasionally aseptic meningitis, flaccid paralysis, rarely encephalitis - EV71

SHOWS TRENDS
But knowing trends we can predict outbreaks, implement early public health intervention measures, etc.

HFMD SURVEILLANCE PROGRAMME STARTED IN MARCH 1998

Fetal outbreaks elsewhere in the region led to fear among the public and the recognition of non-EV71 associated syndromes in late 2000
Holidays influence the shape of the curve

SARS changed the slope of the HFMD epidemiological curve in 2003

Different health seeking behavior of different groups: income differences

Dual Infections Occur Frequently

Dengue Encephalitis?

There is a tendency to accept the first laboratory data in and stop there

18 month girl with DHF and encephalitis: showed DHF IgM seroconversion

2 year old boy with HFMD & encephalitis: An EV was isolated from throat swab; CSF negative for EV
PHYLOGENETIC ANALYSIS IS USEFUL

AND MORE THAN ONE GENOTYPE MAY CO-CIRCULATE DURING AN OUTBREAK

HOSPITALIZATIONS VS OUTPATIENTS

DATA ON JE FROM NATIONAL INSTITUTE OF HYGIENE & EPIDEMIOLOGY, HANOI

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From Dr Nguyen Thu Van, Bilateral JE Meeting, Bangkok, 30-31 March 2006

Fisher's exact test p<0.0001
USAID recognizes that global health issues directly affect the interests of American citizens as well as citizens of under-resourced countries. Programs are needed to stem the spread of infectious disease and to reduce the threat of epidemics. (13) It is necessary to create and support environments which allow for stable populations resulting in a reduction of economic and environmental pressures as well as a reduction in the risk of humanitarian crises. Clear priorities will be established for the global programs of the Centers for Disease Control and Prevention’s (CDC) Global Health Initiative. Additionally, these programs will strive to increase global connectivity ensuring rapid detection and response to emerging health threats.