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**Infectious Disease Study on the Need for Expansion
of Diagnostic, Epidemiological Surveillance, and
Reference Laboratory Capabilities within the Ministry
of Health and Population, Egypt**

A report submitted to the Cairo, Egypt Mission of the United States Agency for
International Development by:

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EXECUTIVE SUMMARY

The Egyptian Reference Diagnostic Center (ERDC) was established with United States Agency for International Development (USAID) and Government of Egypt funding in 1992. The ERDC has expanded as the result of its participation in two projects, the Schistosomiasis Research Project (SRP, 1988-1998) and the Schistosomiasis Vaccine Development Project (SVDP, 1998-2002). The facility has diversified from its original goal of developing schistosomiasis diagnostic tests and vaccines, and has become a state of the art facility capable of supporting the Ministry of Health and Population (MOHP) in studies concerning infectious diseases in Egypt.

In response to the Egyptian MOHP's request to review cooperative in-country activities in infectious diseases, The United States Agency for International Development (USAID/Cairo) asked for a team to investigate the capabilities of public and private sector organizations in Egypt, including departments subordinated to the MOHP, with special reference to identifying and strengthening diagnostic, epidemiological surveillance, and reference-level laboratory needs. In February 2002, this team met with representatives of institutions in Egypt focusing on identifying gaps and/or redundancies in the system; where current and future efforts would be most useful; and where existing ERDC capabilities will require further strengthening, training and expansion based on feasible and economically sound technical methodologies.

The team learned that an infectious disease surveillance program was initiated in Egypt in 1999, and has since made remarkable progress towards establishing a surveillance system and meeting the recognized deficiencies. In three years, the MOHP has written and assembled working documents to start implementing an integrated countrywide surveillance and response network. The team also observed that some units of the MOHP, notably The Egyptian Organization for Biological Products and Vaccines (VACSERA) have done very well in filling the national and regional needs, but would need further assistance in rounding out their programs. In contrast, another MOHP unit, the National Organization for Drug Control and Research, (NODCAR), the regulatory authority for drugs, vaccines, and diagnostics, was observed to be a relatively nascent organization and in need of immediate upgrading and strengthening.

The assessment team identified that the ERDC could both immediately, and over the longer term, contribute to the strengthening of many other MOHP departments. The team therefore recommends (a) that the existing expertise within ERDC be fully utilized by the MOHP, and the Egyptian private sector, (b) that USAID continue to fund and support current and expanded activities of the ERDC, and (c) that in the interest of self-sustainability, and effective operation, the MOHP allow the facility to develop some degree of autonomy.

The first task for the ERDC will be to establish an Office of Human Research Protections (OHRP)-registered Institutional Review Board (IRB) and obtain a Federal-Wide Assurance (FWA) number. The importance of this to Egypt cannot be overstated, because without it, collection of human serum samples, and performing human drug and vaccine

trials under U.S. Federal as well as international funding will not be able to proceed in Egypt, and ERDC will be unable to function in the international arena.

Once this OHRP-registered IRB is established however, ERDC can and should serve as source of new diagnostic technology, and as primary recipient of technology transferred from PATH, CDC, and/or NAMRU-3.

For difficult to diagnose and for other exotic diseases, the ERDC should serve as a reference diagnostic laboratory for MOHP surveillance programs, the Central Public Health Laboratory, and for public/private medical laboratories. ERDC should also, in the longer term, serve as the assay/testing arm of a VTEU within VACSER, and to eventually serve as the regional resource center for diagnostic testing of public health importance.

The ERDC is therefore in a unique position of readiness to meet the challenges, and to be able to provide training to other MOHP units and technical staff from other institutes, as required. However it should not sit back, but expand its scope in order to become a source of "South to South" transfer of technologies, including development of diagnostic tests of commercial interest.

For easy reference, a power point presentation summarizing the recommendations has been attached.

BACKGROUND

Infectious, endemic diseases are a significant public health problem in Egypt, especially in rural areas. In the Ministry of Health and Population (MOHP) report on "Enhanced Surveillance for Communicable Diseases, Annual Summary, January-December 2000" 23 priority communicable diseases of importance (later extended to 26) are given. These include:

- Hepatitis (including infection due to hepatitis B and hepatitis C);
- Meningitis/encephalitis (*S. pneumoniae*, *H. influenzae*, *N. meningitidis*);
- Acute febrile illness (*S. typhi*, *B. abortus*);
- Dysentery (includes *Salmonella* and *Shigella* species);
- Tuberculosis (TB);
- HIV/AIDS;
- Hemorrhagic fever viruses (including West Nile virus);
- Poliomyelitis;
- Neonatal tetanus; and
- Rabies

The Egyptian MOHP has expressed interest in reviewing cooperation between facilities in the public and private sectors in the field of infectious diseases with a view to facilitate and expand services needed. In order to assist the MOHP in this effort the United States Agency for International Development (USAID)/Cairo asked the Program for Appropriate Technology in Health (PATH) to investigate the capabilities of organizations and departments subordinated to the Ministry and their interrelation with special reference to diagnostic, epidemiological and reference needs. A team of five specialists in the areas of diagnostics, vaccine development, and private sector promotion, representing Centers for Disease Control and Prevention (CDC), Program for Appropriate Technology in Health (PATH), Ain Shams University, and the World Health Organization (WHO), gathered in Cairo in February 2002 to collect information, discuss activities with the institutions concerned and their representatives to form and draft an opinion. The study team met with representatives from the Egyptian Reference and Diagnostics Center (ERDC), various other units of the MOHP including the Central Public Health Laboratories (CPHL), the National Organization for Drug Control and Research (NODCAR), the Egyptian Organization for Biological Products and Vaccines (VACSERA), Naval Medical Research Unit-3 (NAMRU-3), Schistosomiasis Vaccine Development Program (SVDP), and seven different private entrepreneurs in the field of commercial diagnostics. The team focused on which coordinated efforts might be useful and where existing capabilities of ERDC may require strengthening and expansion based on feasible, economically sound technical methodologies needed to sustain their current functions. Emphases were placed on:

- Capabilities and needs for priority diseases
- Gaps in the system
- Redundancies

- Institutional strengthening
- Individual training

Parties Concerned

With reference to the need for strengthening diagnostic and epidemiological surveillance capabilities, a number of MOHP activities were identified such as the Epidemiology and Surveillance unit (ESU), the HIV/AIDS Control Program, including several MOHP institutions, which might benefit from closer interaction and mutual assistance. This list also included United States-based institutions, international organizations, foundations, national academic institutions, research institutions and private sector activities. The main interacting Egypt-based organizations include the following:

- Egyptian Reference and Diagnostic Center (ERDC)
- MOHP Central Public Health Laboratories (CPHL)
- National Organization for Drug Control and Research (NODCAR)
- Egyptian Organization for Biological Products and Vaccines (VACSERA)
- Naval Medical Research Unit (NAMRU)-3

Relevance to USAID Health Office current plans

The "Combating Endemic and Emerging Diseases" (CEED) project, initiated by USAID/Cairo in 1996 supported the Schistosomiasis Research Project (SRP) and the follow-up Schistosomiasis Vaccine Development Project (SVDP) in order to assist national control efforts to develop new control tools against schistosomiasis, which was then the major public health problem in rural Egypt. The CEED project also included work on hepatitis C, a major emerging disease of concern in Egypt, and control of HIV/AIDS. USAID/Cairo intends to phase out its aid over the next seven years and the strategic objectives (SO 20) of the Health Office during this time. Strategic Objective 20 (SO 20), "Healthier, Planned Families" works towards establishment of sustainable basic health services which will be promoted by strengthening the health sector capacity and improving policy and regulatory authority performance in the health care system by:

- building on USAID's previous country investments;
- expanding surveillance and control efforts for the at-risk population;
- strengthening the capacity of MOHP to reach sustainable proficiency; and
- boosting institutional and commercial involvement.

To achieve Healthier Planned Families, the MOHP and USAID/Cairo need to address the problem of providing prompt and accurate diagnosis and adequate treatment of infectious diseases as part of sustainable basic health services. Additional tools, however, are needed for diagnosis, disease surveillance, and to identify modes of transmission. The specific contributions would include:

- a sustainable reference-level, diagnostic laboratory with a capability to accurately diagnose and report not only high-priority infections but also parasitic infection and other diseases of concern;
- a sustainable program for product development and transfer of reference level as well as simple and rapid diagnostic tests for priority infectious diseases;
- diagnostic test production and distribution in the private sector in Egypt; and
- provision of quality diagnostic tools for clinicians.

CLIENTS, COLLABORATORS, AND PARTNERS

Egyptian Reference Diagnostic Center (ERDC)

ERDC is situated within the compound of VACSERA and headed by Dr. Maged Al-Sherbiny, Scientific Director and Dr Ahmed Osman, Deputy Director. The current staff consists of four post-doctoral fellows, six Ph.D. students, 13 M.Sc. students, four medical technologists and four technicians under the direction of the Scientific Director. The ancillary staff includes an administrator, a legal advisor, a maintenance engineer, a maintenance clerk, a radiation and safety supervisor, a data-base specialist, a biostatistician, a MIS specialist, accountants, executive secretaries, store keepers, drivers, and cleaning clerks. ERDC has had a long-term collaboration with the Egyptian-American Schistosomiasis Research Program (SRP) and its follow-up program the Schistosomiasis Vaccine Development program (SVDP). It is currently the lead national agency in the effort to produce a GMP-grade *S. mansoni* vaccine. Fields of expertise include molecular biology and immunochemistry capabilities. It has radioisotope facilities, sterilization and tissue culture units and is proficient in hybridoma technology and testing using ELISA and immuno-chromatographic strip (ICS) formats making it capable of production of low-volume, clinical grade rapid assays.

As an independent research center within the MOHP, the ERDC currently has the capability to perform a number of services and functions to serve as a resource to other departments within the MOHP and other public- and private sector organizations within Egypt. In addition, ERDC has been recognized as a valuable collaborator internationally and has begun to attract external sources of funding, which can be a key to developing sustainability.

To achieve sustainability by 2009, ERDC must now continue to expand their current collaborations and will also need to actively seek and establish additional collaborators in both industry and the private sector. As a "center of excellence" in Egypt, the following is a partial list of services, resources, and functions that ERDC could provide to interested parties:

The Egyptian Organization for Biological Products and Vaccines (VACSERA)

VACSERA, a unit of the MOHP, is responsible for vaccine production to meet the needs of Egypt. VACSERA has in recent years not only met national needs, but is now exporting vaccines and other related products to countries in the Middle East region.

VACSERA is diversifying and produces biological products in addition to vaccines ranging from blood components to intravenous fluids and diagnostic reagents such as anti-O, tuberculin, and horse antisera. In addition, it provides many other functions including a blood bank, and the WHO-sponsored regional reference center for diagnosis of poliovirus.

VACSERA's director Dr. M. Abaddi has expressed considerable interest in local production of rapid diagnostic tests. Since ERDC plans to expand and enhance their product development capabilities, especially in rapid test development, ERDC may be able to provide their know-how to VACSERA by technology transfer. This would allow VACSERA to scale up and manufacture priority test kits starting with HCG (pregnancy), hepatitis B, and hepatitis C. Development of other test kits for infectious agents on the MOHP priority reporting list could also be considered. However, it is important to note that no organization, public or private, has been selected by ERDC as a technology transfer recipient at this time.

Industry sources interviewed by the team indicated there is a considerable market for rapid tests in Egypt, ranging into the millions of tests per year, especially tests for diagnosis of pregnancy (HCG) and blood viruses (hepatitis B, hepatitis C, and HIV). Since there are no local manufacturers, the quality of imported tests is often variable, and imports represent a net loss of valuable foreign exchange. Instead, if local production is established, quality can be better controlled, and the potential export of tests could instead be a gain in foreign exchange. ERDC could also assist in designing and validating a production facility for rapid test kits, and to ensure that efficient manufacturing protocols are implemented to minimize waste and maximize production efficiency. Local production of reasonably priced, but high quality rapid tests would represent a considerable advance over the current situation.

ERDC is capable of providing quality control (QC) for diagnostic kits in the initial stages of scale-up and production to determine relative sensitivity, specificity, stability, and overall quality, and to compare the product performance with other manufacturers. This monitoring function can continue as long as it is necessary to ensure consistent quality production, but this function can be phased out when VACSERA's capabilities for providing their own effective manufacturing QC are established and validated.

ERDC is currently serving as a needed research and development resource to VACSERA for development of vaccines for hepatitis C virus, tuberculosis, and typhoid fever. Their development role should expand if they make substantial progress in their initial efforts. ERDC can also provide a reference QC function for vaccines in development and initial production steps to determine their efficacy, potency, and/or immunogenicity, and could also contribute towards establishment of a vaccine and therapeutics evaluation unit (VTEU) within the MOHP that VACSERA will require as its vaccines are developed for clinical trials.

Egyptian Ministry of Health and Population (MOHP)

Because a key function of the ERDC will be to serve and collaborate with units of the MOHP including VACSERA, the Central Public Health Laboratory, the Infectious Disease Surveillance Unit, and the HIV/AIDS Control Program, it will be essential to establish a functional Office of Human Research Protections (OHRP)-registered institutional review board (IRB) to ensure the ethical treatment and protection of human subjects. This IRB can be used for MOHP and academic requirements. Internationally, IRB review and approval of experimental protocols is now the accepted process that needs to be addressed before clinical trials can start. If there is no functioning IRB, ERDC and other institutions cannot receive many sources of international funding, including funds from The UK-based Wellcome Trust, and the United States NIH, and CDC. Currently in Egypt, only NAMRU has an OHRP-approved IRB, but it is not easily accessed by outside organizations and is mainly used for review of NAMRU internally funded projects. The functions and potential interactive activities of ERDC with the various units of the MOHP are summarized below:

MOHP - National Organization for Drug Control and Research (NODCAR)

NODCAR appears to be a nascent organization that currently appears to be in need of additional expertise and funding to allow it to assume its expected role as the premier regulatory agency governing approval of vaccines, therapeutic drugs, and diagnostic test kits in Egypt. The NODCAR facilities are currently undergoing a major renovation, which will upgrade the laboratory and (hopefully) their testing capabilities. Because NODCAR must retain its impartiality, it cannot receive external funding directly or indirectly to strengthen their operations. Currently, NODCAR's testing of diagnostics is confined to routine variance and stability analyses. There is no current capability for evaluation of sensitivity and specificity. Upon approval, diagnostic tests receive a registration number. ERDC is well poised to provide advice and expertise on improved and/or expanded reference level testing methods, as needed, for vaccines and diagnostic test kits.

MOHP - Epidemiology and Surveillance Unit (ESU)

Dr. Mohamed Ahmed Abdel-Nasser heads the ESU of the MOHP. Concerted efforts in infectious disease surveillance effectively began only in 1999 after an in-depth review of the existing system in late 1998 by representatives of WHO, USAID, CDC, and NAMRU. This analysis determined that surveillance was not a high government priority. There were a lack of existing guidelines, no effective data gathering and management systems, no integration of vertical programs, limited laboratory capabilities, and no prioritized list of notifiable diseases. In the intervening three years the ESU, with assistance from CDC, NAMRU, USAID and others have established a Surveillance Working Group and have made remarkable progress towards establishing the surveillance system and meeting the recognized deficiencies. The ESU has written and assembled a number of working documents to bridge these gaps and to start implementing an integrated national surveillance and response network.

The ERDC could provide technical advice on improved methods of diagnostic testing for the ESU when requested. For example, in the 2001 National Guidelines for

Communicable Disease Surveillance document, the Widal test is listed as the reference method for diagnosis of typhoid fever (*Salmonella typhi*). Recent publications have shown the Widal test to lack the necessary sensitivity and specificity to be truly useful as an accurate indicator of infection, and there are more accurate methods recently developed that can be applied to surveillance and diagnosis, which are now commercially available.

ERDC could also perform specialized, non-routine, research-level epidemiological testing to confirm diagnosis of priority diseases. For example, they could provide Western blot or rapid strip test analysis of sera to speciate schistosomiasis infections, or provide serological or molecular typing of hepatitis C virus specimens. These analyses will assist the ESU in tracking of outbreaks and in identifying their origins.

ERDC should, in discussion with the ESU, identify and prioritize the diagnostic tests on the MOHP list of diseases for use at lower levels of the surveillance system. If new tests are currently available, ERDC could arrange to import and evaluate the tests. If the tests are not available, ERDC may consider developing, commercializing, and introducing appropriate tests, and provide training in the use of these simple/rapid tests to improve surveillance.

MOHP - HIV/AIDS Program

While prevalence of HIV and AIDS is low in Egypt when compared with the sub-Saharan African countries, control and monitoring efforts are nevertheless very important to ensure that a major epidemic does not develop. There should be an important role for ERDC in contributing to and strengthening this program. The central laboratory has already requested ERDC to perform back-up Western blot confirmatory testing. ERDC should continue in this capacity because it allows more rapid return of results. ERDC could even produce the Western blots needed for this activity in their laboratory, thus saving the cost of importing and purchasing expensive kits. In addition, Dr. Nasr Sayed, Director of the HIV/AIDS program, indicated that ERDC could evaluate commercially available HIV serological test kits annually and compare them for sensitivity, specificity, and ease of use on panels of local sera from Egypt. This would remove the burden of annual testing from the HIV/AIDS Program and have the comparative testing performed to high standard.

ERDC could also perform non-routine, reference level tests for epidemiological research. For example, genotyping of HIV strains is important in order to determine if the proportion of viral clades has shifted in new cases. If so, this would indicate new routes or sources of transmission. ERDC could also evaluate and recommend new diagnostic tests such as those using saliva or urine as a specimen and could evaluate and introduce advanced testing methods as needed. For example, with numbers of patients in need of anti-retroviral therapy, monitoring tests such as those for CD4 lymphocyte counts and p24 viral load will be needed. ERDC could also participate in sentinel surveillance studies by testing sera from high-risk groups to determine the serological prevalence of HIV.

MOHP – Central Public Health Laboratory (CPHL)

The CPHL, under the direction of Dr. Magda Rakha, is a sprawling laboratory complex that is well-equipped, adequately staffed, and charged with many different public health tasks. These include general testing for environmental toxins, testing foods for microbial contamination, diagnosis of cancer, blood virus screening, histological analyses of tissues, and general reference-level diagnostic testing for infectious diseases. Their personnel perform complex methodologies using sophisticated equipment and devices that are updated to international standards. The CPHL also supports the reference testing laboratory for the national infectious disease surveillance program. Despite the CPHL's comparative wealth of resources, including high-volume diagnostic equipment and cutting-edge technologies, ERDC could still be of assistance. ERDC can perform back-up identification and esoteric or seldom-seen pathogens and in diagnosis of their diseases that are not cost-effective for CPHL to handle on a routine basis, including confirmatory testing for HIV and other blood viruses. ERDC could identify or produce, then evaluate, and introduce newer and more cost-effective diagnostic kits and methods for priority diseases to improve the efficiency and accuracy of the central lab. ERDC could also train CPHL personnel in the use of the new techniques or devices.

International and Local Universities

ERDC staff hold university positions at the University of Cairo. As a result, ERDC already has a role as a training resource for technicians, graduate students, and postdoctoral trainees. Some trainees are retained by ERDC, but others are hired by VACSERA and other government institutes thereby contributing to the pool of trained scientific manpower in the public sector in Egypt.

ERDC can also serve as an applied research center for collaboration in academic research, and would be capable of technology assessment, development, transfer, and introduction of potential diagnostic reagents or products. They would be encouraged to consider and assisted, if necessary, in applying for international grants. ERDC should be able to provide their OHRP-approved IRB for approval of clinical protocols to assist their colleagues in academia and could supply appropriate reference reagents for research applications. ERDC has already established initial collaborations with some relevant universities in the U.S. and U.K. such as Maryland, Oxford, and Glasgow, and should seek additional academic links that would allow them to increase their level of international research funding.

Program for Appropriate Technology in Health (PATH),

PATH, based in Seattle, WA, is an international non-profit organization whose mission is to improve health, especially the health of women and children. PATH identifies, develops, and applies appropriate, innovative solutions to public health problems. PATH exchanges knowledge, skills, and technologies with governmental and non-governmental partners in developing countries and with groups in need elsewhere. PATH plays key roles in linking the public and private sectors by providing technology-related services

and solutions. PATH works with international development agencies, governments, other NGOs, and private industry.

PATH's previous collaborations with ERDC include the SVDP funded by USAID under the HealthTech program, and initial technology development and transfer to ERDC for rapid test production. PATH is willing to continue collaborative efforts with ERDC in technology development and transfer. PATH's ongoing rapid diagnostics development program is internationally recognized and includes development, evaluation, and introduction of tests for infectious diseases such as falciparum malaria, diphtheria, syphilis, tuberculosis, HIV, other STDs, and hepatitis B. PATH's facility includes a 2,500 square foot laboratory in which to conduct diagnostics research, product development, and technology transfer. It includes a dedicated area for development of molecular testing, and can handle clinical specimens, potential pathogens, and undefined sera or blood. The laboratory contains a range of technical, product development, and information-processing equipment to support activities, and a facility for pilot production of rapid tests, which can also be used for training in technology transfer.

Naval Medical Research Unit (NAMRU)- 3

NAMRU, a regional research facility and a unit of the United States Navy in Cairo, has conducted basic and applied research in infectious diseases in Egypt and the region for the last 50 years. They possess excellent facilities for viral and bacterial isolation, serve as a reference laboratory, and set up and manage vaccine and therapeutic trials in Egypt. They employ U.S. military as well as CDC and local staff to conduct their studies and are funded by USAID as well as the U.S. Department of Defense. NAMRU has the only OHRP-registered IRB in Egypt, allowing them to perform clinical trials with U.S. funding. They have provided significant input into developing the national surveillance system now being implemented, including a computerized reporting system, and supply rapid response capabilities to investigate outbreaks of disease. They represent another significant resource to Egypt in the identification and control of infectious diseases. ERDC and NAMRU have interacted in the past, have shared equipment and supplies that are often difficult or expensive to obtain in Egypt, possess complementary know-how, and should continue to explore additional ways of collaboration.

Centers for Disease Control and Prevention (CDC), Atlanta, Georgia

The ERDC was established in 1993 with the collaboration and guidance of the CDC under the Schistosomiasis Research Program. Its initial purpose was to perform as a reference laboratory for diagnosis of schistosomiasis. The ERDC has provided CDC with a controlled field environment for testing of new schistosomiasis diagnostics and other control methods under defined conditions, and should continue to expand this role to additional testing and evaluation for other disease entities in the future.

Other Regional and International Organizations

With expansion into other infectious disease entities, ERDC has the potential to become a recognized entity in international infectious disease research. For example, ERDC is currently under consideration for appointment as a collaborating center for WHO. ERDC, with training from PATH, CDC, and other organizations, can provide technical

development expertise and product development of simple/rapid and reference level tests to address local or regional problems. A practical example of this was the application of the serological test for shistosomiasis antibodies developed by ERDC for application in regions of low endemicity. The use of this test in Morocco was instrumental in demonstrating that specific control methods implemented there were indeed effective. They are therefore a state of the art laboratory that can be made increasingly available as a resource for international collaborations in diagnostics and vaccine development and run clinical and field evaluations.

Private Sector

Private Sector - International

ERDC is currently interacting and collaborating with United States and large, internationally based commercial companies such as Bachem Laboratories, Chiron, and Merck. In the future ERDC could expand its role as a regional resource in development of diagnostic tests and vaccines, in performing clinical/field evaluations, and in providing a world-class laboratory for international collaborations. By doing so, ERDC is poised to attract significant levels of funding.

Private Sector - Egypt

As an advanced technology provider of both diagnostic reference services and diagnostic assay development, ERDC may interact with two primary segments of the private sector in Egypt, including private sector clinical laboratories and private sector manufacturers of diagnostic reagents and test kits.

ERDC's general capabilities in vaccine development and biotechnology may also be of interest to other private sector vaccine or pharmaceutical companies, although at this time the only Egyptian company with a broad interest in collaborating with ERDC is VACSERA, a state owned institution.

1. ERDC and Private Clinical Laboratories. In addition to the diagnostic laboratory services offered through the MOHP system, there are numerous private clinical laboratories in Egypt of different sizes. This system is relatively robust. These laboratories provide a wide range of clinical services to private physicians, clinics and hospitals. The private clinical laboratory market in terms of both number of samples processed and value of services provided is dominated by a few larger laboratories who each have their own network of laboratories in the major cities of Egypt. One example is Al-Borg in Heliopolis who routinely process 300+ samples per day. The larger firms collectively provide around 70% of the total volume of private lab tests in Egypt and, in large part, are comparable in terms of technical sophistication and process automation, with many European or North American laboratories. At the other end of the scale, there are over 3,000 smaller private clinical laboratories that serve basic needs in smaller towns and villages in Egypt. Many of these labs process fewer than 50 samples per day and rely primarily on manual tests for chemistries and use non-instrumented processes. ERDC is certainly not redundant with the network of private clinical laboratories. The clinical labs provide fee-based services to support front-line physicians, clinics, and hospitals while ERDC focuses on high-level

reference diagnostic support primarily to the MOH system. The more likely way in which ERDC can impact/improve this system is through development of new diagnostic tests which will become available for use in private clinical labs. However, this will be an indirect link, as ERDC itself does not seek to become an ongoing commercial supplier of tests. ERDC will partner/collaborate with one or more companies able to produce and supply tests to all public and private market segments in Egypt.

2. ERDC and Private Sector Manufacturers of Diagnostic Reagents and Test Kits. While local production of generic pharmaceuticals is well established in Egypt, there has been minimal development of local production of clinical diagnostic reagents and diagnostic test kits. Almost all products are imported. Major multinational companies such as Abbott and Hitachi import reagents and tests for their sophisticated, proprietary instruments. Rapid diagnostic tests purchased by the MOHP are all imported from whichever company offers the lowest possible pricing during a given tender period. This has led to an increase in importation of rapid kits from unregulated, little known producers in China and other low-cost-of-business countries. Local production of diagnostic reagents and kits is not well established in Egypt, in part because the pricing structure and multiple supplier regulations of the GOE, that encouraged the local production of drugs, was not extended to diagnostic reagents and kits. The study team identified just one private sector company in Egypt, Diamond Diagnostics (DD International). They hold the first manufacturing license for diagnostics in Egypt and are currently producing and selling diagnostic reagents for clinical chemistries. To the best knowledge of the team and the many local industry and government experts interviewed, there are no local commercial producers of rapid diagnostic tests. One or two importers undertake local packaging of pre-produced rapid tests.

There are, however, signs that local production of reagents, and ultimately rapid test kits, are about to establish a stronger presence in Egypt. This will be due primarily to the work of Diamond Diagnostics to:

- Lobby and educate the MOHP to establish appropriate manufacturing licensing procedures within NODCAR for reagent and test kit production.
- Expand their product line to include reagents for automated test systems

Starting later this year, Diamond Diagnostics will begin competing for annual MOHP tenders for supply of reagents. If Diamond is successful in winning a portion of MOHP tender for reagents, this could rather rapidly stimulate other companies to shift from importing to local production.

ERDC and private sector manufacturers of reagents and test kits

Given the very nascent state of local production of reagents and test kits in Egypt and the relatively limited capacity for these firms to undertake new product development, it is clear that ERDC can play a unique role in developing products.

Egyptian Market for Rapid Tests

If rapid tests can be produced locally and at reasonable prices, they would have a cost advantage over imports since MOHP procurement would favor local production. If a suitable commercial partner can be identified that is willing to invest in the project, ERDC could assist in establishing local production, designing and validating a production facility, and to ensure that efficient production protocols are written and implemented to minimize waste and maximize production efficiency.

As part of the assignment, the team also made preliminary research into the market for rapid tests in Egypt. Among the various private and public sector experts interviewed there was a strong consensus on the four most widely used rapid tests:

- Hepatitis C antibody detection
- Hepatitis B surface antigen detection
- HIV 1+2 antibody detection
- HCG detection (pregnancy test)

The first three are primarily used in those blood screening applications where more traditional ELISA tests are not available. The HCG pregnancy tests are most often used in clinical settings.

There was a lack of consensus on the actual current market size for rapid tests. Market estimates of interviewees from the private sector ranged from a low of around 300,000 total units (all 4 tests) to a high of over 10,000,000 tests per year. It was the expert team's estimate that current use of rapid tests in both the public and private sector markets in Egypt is on the order of two to four million tests per year. Further defining this estimate would require a more detailed study.

The trends for rapid tests in the market were clearer, and the consensus is:

- Rapid tests are more popular (and also needed) in smaller labs and rural areas that lack infrastructure to do automated testing
- Price competition is fierce.
- All products are imported (at this time)
- Rapid tests could serve an important role in field-based preliminary screening of blood before it is brought to central blood bank facilities for more detailed testing.

Tasks recommended for the ERDC

Establish urgently an Office for Human Research Protection's (OHRP)-registered Institutional Review Board (IRB), and obtain a Federal Wide Assurance (FWA) number for MOHP/ERDC.

There is currently only one OHRP-registered IRB in Egypt, belonging to NAMRU-3. Recently, an international requirement has been implemented covering all research on

human subjects. Research protocols must be reviewed in advance and approved by an OHRP-registered IRB in order to receive federal funding. Institutions that are involved in human subjects research must also be registered and receive a FWA number. FWA numbers are required for all cooperative human subjects research funded by the U.S. Federal Government and many donor organizations. To illustrate its importance, the U.S. Government has cut off its funding to institutions that failed to comply with this regulation. Deferring to an U.S.-based IRB with a FWA is no longer adequate for cooperative research. The team strongly recommends the immediate formation of OHRP-registered IRB and acquisition of a FWA number within the ERDC on behalf of the MOHP of Egypt. This IRB can then be made accessible to all MOHP and university protocols. A fee for services structure can also be devised to defray the cost of this operation. Clear procedures and training for doing this is available at the OHRP website (<http://ohrp.osophs.dhhs.gov>). Significant help can also be derived from professional organizations for IRB training. Without an OHRP-registered IRB and FWA, the ability of the ERDC to utilize U.S. funding, or even to collect reference sera will be jeopardized.

Serve as source of new diagnostic technology and the principal interface with CDC and NAMRU

- Because of its previous collaboration history, its extensive world-class equipment, and availability of trained personnel, the ERDC is the logical first point of contact in all technology transfer concerning diagnostic assays and vaccine efficacy testing. Because of previous exchanges of personnel, and regular interactions, the ERDC is also the most effective primary Egyptian interface with CDC and NAMRU, since both are organizations with broad interests and capabilities in diagnosis, epidemiology, and disease surveillance.
- Because of its location within the MOHP and VACSERA, and with connections to local medical institutions, the ERDC is uniquely positioned to adapt the sophisticated technologies it has acquired to formats and performances appropriate to the local needs of Egypt. The ERDC can also pilot test and modify transferred technologies and diagnostic tests.
- Once test modifications and adaptations are completed, and the test produced on a pilot basis with satisfactory outcomes, the ERDC can then transfer the technologies to local commercial companies for production or to an organization such as the VACSERA for production scale-up and deployment.

Serve as reference diagnostic center for MOHP surveillance programs, public and private medical laboratories.

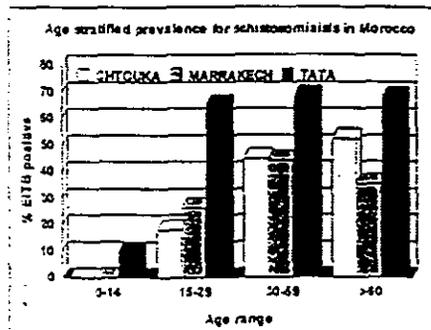
- The ERDC is not equipped or staffed to perform routine surveillance testing, nor is it a regular diagnostic laboratory for clinical samples. However, it is uniquely qualified to serve in a reference diagnostic role. It can provide quality assurance (QA) testing and samples and develop a QA program for other laboratories.
- It can also perform technically difficult and advanced testing methods, especially for low-volume diagnostic assays for rare and exotic diseases that are difficult for other private, public, and MOHP laboratories to maintain in their routine repertoire.

Serve as the assay and testing arm of a VTEU (Vaccine Testing and Evaluation Unit) within VACSERA

- The establishment of a VTEU within the ERDC is currently difficult to justify and would currently require too significant an investment of ERDC staff and funding resources. The full utilization of the VTEU will depend on the availability of vaccines for testing. While this level of resource investment would be difficult to justify for the ERDC alone, it would certainly be within the scope and mandate of VACSERA.
- However, the ERDC's advanced diagnostic and testing capabilities (in terms of equipment and trained personnel) certainly makes it the logical unit to conduct the testing and assay functions that are required of the VTEU. We recommend, therefore, that the ERDC perform the assay and testing function of the VTEU and recommend that VACSERA organize and manage the VTEU.
- In addition, when an OHRP-registered IRB and FWA becomes a reality within the ERDC, this will be another vital service and function for all future vaccine testing programs for the VTEU, VACSERA, and other MOH programs.

Serve as the regional resource center for diagnostic tests of public health importance

- In the initial development of the ERDC, its structure, training, and equipment were patterned after similar laboratories in the CDC. As a result, ERDC has now matured into a competitive, world class laboratory as evidenced by its ability to attract international funding from donors such as the Wellcome Trust. Many of its technologies and diagnostic assay repertoire as also of world standard and state of the art. Furthermore, because of its location in Egypt, test formats are often adapted into a locally relevant configuration. This added value will allow the ERDC to make the tests they will offer much more valuable and practical to



- A clear example of this asset was demonstrated in a recent survey conducted by the ERDC for the MOH of Morocco, which was mediated through WHO. In this project the ERDC, using diagnostic technologies transferred from the CDC, was able to show that two of three Moroccan districts historically endemic for schistosomiasis have achieved "elimination" of this disease

sometime during the last 14 years (Figure). This conclusion was based on the fact that there was an absence of serologically positive children found that were less than 14 years of age in two of the districts. The test used was the enzyme immunoassay transfer blot (EITB) which has exquisite sensitivity and specificity for detecting transmission in children that are otherwise not detectable by traditional tests. This project, because of the direct involvement by the ERDC, was completed with a minimum of cost, time, and with ethical and cultural relevance. This is a clear success in the "North to South" to "South to South"

model of technology transfer. USAID and Egyptian MOHP should be proud of facilitating this success story. The ERDC should promote other opportunities of this kind of regional technology.

Summary of recommendations and task list for the ERDC:

1. Establish a host facility for an OHRP-registered IRB and obtain a FWA number.
2. Serve as source of new diagnostic technology.
3. Serve as primary recipient of technology transferred from CDC, PATH, and/or NAMRU-3.
4. Provide training to MOHP and technical staff from other institutes as required.
5. Serve as a reference diagnostic center for MOHP surveillance programs, and public/private medical laboratories.
6. Serve as assay/testing arm of a VTEU within VACSERA.
7. Serve as the regional resource center for diagnostic tests of public health importance.
8. Source of "South to South" transfer of technologies.
9. Source of diagnostic tests of commercial interest.
10. Obtain ministerial decree as a discrete entity capable of receiving external funding and negotiating commercial contracts

Appendix I
ERDC capabilities

The ERDC is capable of performing infectious disease research and development activities that are comparable to units of similar size and function in the United States or Europe. The following summarizes their programs, laboratory groups or units, and areas of specialization:

- a- Quality control unit for the national schistosomiasis control program (NSCP), to quality control the performance of NSCP nationwide through the parasitic evaluation of representative samples from all Egyptian governorates. The unit also assesses the performance of NSCP teams and provides evaluation reports to the central management of the program.
- b- Immunochemistry laboratory, equipped with an FPLC to fractionate and purify antigens and antibodies. The unit is also equipped with protein electrophoresis units to evaluate protein profiles and reactivities.
- c- ICS production unit, to produce immunodiagnostic strips for infectious diseases.
- d- Data center to handle ERDC's database files and perform appropriate statistical analysis and computer graphics.
- e- ELISA unit, to measure antibody responses in potency tests and cytokine responses in *in vitro* cellular studies.
- f- Tissue culture unit, to perform proliferation and cytokine production assays in sterile conditions. This unit, with upgrading, could be used to isolate and culture viruses of medical interest.
- g- Clinical examination and phlebotomy unit, equipped with an ultrasound-scanning machine and a photo documentation camera.
- h- Clinical laboratory unit, for the E-VTEU equipped with a haematology counter, a clinical chemistry auto analyzer and a flow cytometer to clinically evaluate vaccinees during clinical trials.
- i- Pilot vaccine production facility, equipped with a 10-liter fermentor. This facility was used to produce small batches of the experimental schistosome vaccine Paramyosin for pre-clinical evaluation.

- j- **Molecular biology facility**, equipped with sophisticated RNA and DNA equipment to purify, sequence and measure nucleic acids. It also clones and expresses different target antigens.
- k- **Hybridoma facility**, equipped with cell culture incubators and laminar flow hoods that are capable of producing and raising hybridomas making different monoclonal antibodies of clinical or medical interest. The unit is also equipped with an automated ELISPOT reader for cytokine evaluation.
- l- **Radioactive isotope facility**, equipped with a state-of-the-art beta radiation counters to evaluate newly synthesized DNA by thymidine uptake in cellular proliferation assays.
- m- **Other supporting infrastructure**, such as storage, freezing, liquid nitrogen, washing, and sterilization facilities.

Appendix II

“SWOT” Analysis of ERDC

<p>STRENGTHS</p> <ul style="list-style-type: none"> • State of art facilities for advanced diagnostic reference testing, test development, and associated support of vaccine research • Internationally recognized scientific skills • Broad base of interactions—other MOHP units, USAID, CDC, NAMRU, and additional regional and international groups • Able to attract and train top young scientific talent 	<p>WEAKNESSES</p> <ul style="list-style-type: none"> • Capabilities not well understood by all groups in MOH that might benefit from collaboration with ERDC • Not officially recognized as an MOHP “Unit of Special Nature” with institutionalized authorization to self-manage budgets, receive outside grants, subcontract public or private sector organizations to perform work or enter technology transfer agreements with commercial collaborators • Possibly dependant on key leader
<p>OPPORTUNITIES</p> <ul style="list-style-type: none"> • Well positioned to leverage strong human capital and technology infrastructure to advance capabilities of infectious disease diagnosis and surveillance • Needs have been established for product development and local production of diagnostic tools for infectious diseases important to Egypt and the region • With expanded scientific and diagnostic capabilities, ERDC could fill the immediate and longer-term needs of other MOHP units and the private sector • Increase diversity of funding by collaborating with national, regional, and international groups 	<p>THREATS</p> <ul style="list-style-type: none"> • Possible desire by other groups to dominate access to and use of ERDC scientific capabilities • As ERDC brings in more external funding, other groups may attempt to claim share of revenue

Appendix III

List of Meetings 3-14 February 2002

MOHP	Dr. Said Ohn, Dr. M. Abdel-Nasser (DSU), Dr. Nasr Sayed- (HIV/AIDS Program)
CPHL	Dr. Magda Rakha
ERDC	Dr. Maged Al-Sherbiny, Dr. Ahmed Osman
SVDP Secretariat	Dr. Mohamed Mostafa and Dr. Taha El-Khoby
PATH	Dr. Alan Fenwick
VACSERA	Dr. M.A. Abbadi, Dr. Ahmed Hamdi
NODCAR	Dr. Sohair A. Ibrahim
USAID	Dr. Sameh Al-Gayar, Dr. Emad Adly Yanni, Mark A. White
NAMRU-3	Capt. Edward Antosek, Capt. Mark Wooster, Dr. Hoda, Mr. Hossam, Dr. Sam Lewis, Dr. Frank Mahoney, Capt. Robert Frenck, Cdr. Earhart, Dr. Mostafa Mansour
Private Sector	
Biomed Egypt	Dr. Mohamed Amin, Mr. Mahmoud Abu-Zaid, Dr. Mahmoud Hanafy
Diamond Diagnostics	Dr. Mohamed Said, Dr. Khaled Raafat
Ultra Group	Mr. Wagih Farag Aly, Mr. Adel Abdel Magid
Abbott/Egypt	[Maged to add name]
Supplies company	[Woman visitor; Maged to add name]
"Old Folks Diagnostics"	[Visit to facility – retired ex-VACSERA scientist – Maged to add names and company]

Appendix IV

Assessment Team

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