PD-AAQ-921

AGENCY FOR INTERNATIONAL DEVELOPMENT

PROJECT DATA SHEET

1. TRANSACTION CODE: A (A = Add, C = Change, D = Delete) — Amendment Number: ISN 38715

DOCUMENT CODE: 3

2. COUNTRY/ENTITY

3. PROJECT NUMBER: 936-5935

4. BUREAU/OFFICE: S&T/Health

5. PROJECT TITLE (maximum 40 characters): Diagnostic Technology Development

6. PROJECT ASSISTANCE COMPLETION DATE (PACD): MM 12 DD 31 YY 92

7. ESTIMATED DATE OF OBLIGATION (Under 'B.' below, enter 1, 2, 3, or 4)
A. Initial FY 85 B. Quarter 4 C. Final FY 91

8. COSTS ($000 OR EQUIVALENT $1 =)

A. FUNDING SOURCE	FIRST FY 85 B. FX	C. L/C	D. Total	LIFE OF PROJECT E. FX	F. L/C	G. Total
AID Appropriated Total			600			10,000
(Grant)	( )	( )	(600)	( )	( )	(10,000)
(Loan)	( )	( )	( )	( )	( )	( )
Other U.S. 1.						
Other U.S. 2.						
Host Country						
Other Donor(s)						
TOTALS			600			10,000

9. SCHEDULE OF AID FUNDING ($000)

A. APPROPRIATION	B. PRIMARY PURPOSE CODE	C. PRIMARY TECH. CODE 1. Grant	2. Loan	D. OBLIGATIONS TO DATE 1. Grant	2. Loan	E. AMOUNT APPROVED THIS ACTION 1. Grant	2. Loan	F. LIFE OF PROJECT 1. Grant	2. Loan
(1)	513	530				10,000		10,000	
(2)									
(3)									
(4)									
TOTALS						10,000		10,000	

10. SECONDARY TECHNICAL CODES (maximum 6 codes of 3 positions each)

11. SECONDARY PURPOSE CODE

12. SPECIAL CONCERNS CODES (maximum 7 codes of 4 positions each)

A. Code	BR						
B. Amount	10,000						

13. PROJECT PURPOSE (maximum 480 characters)

To develop simple, inexpensive diagnostic technologies for use at the primary health care and community level.

14. SCHEDULED EVALUATIONS
Interim MM 10 YY 88 MM 10 YY 90 Final MM 01 YY 91

15. SOURCE/ORIGIN OF GOODS AND SERVICES
☒ 000 ☐ 941 ☒ Local ☐ Other (Specify)

16. AMENDMENTS/NATURE OF CHANGE PROPOSED (This is page 1 of a ____ page PP Amendment.)

17. APPROVED BY
Signature: Ann Van Dusen
Title: Ann Van Dusen, Acting Director for the Office
Date Signed: MM 04 DD 04 YY 85

18. DATE DOCUMENT RECEIVED IN AID/W, OR FOR AID/W DOCUMENTS, DATE OF DISTRIBUTION
MM DD YY

AID 1330-4 (8-79)

Project Authorization

Name of Country: Interregional

Project Title: Diagnostic Technology Development

Project Number: 936-5935

1. Pursuant to Section 104 of the Foreign Assistance Act of 1961, as amended, I hereby authorize the centrally-funded project Diagnostic Technology Development, involving planned obligations not to exceed $10 million in grant funds over a seven year period from the date of authorization, subject to the availability of funds in accordance with the A.I.D. OYB/allotment process, to help in financing foreign exchange and local currency costs for the project.

2. The project will provide funds to develop and transfer simple cost-effective diagnostic technologies for use in LDCs which will permit accurate assessment of both individual and community disease burden. Activities of the project include: 1) identification of the needs and priorities for development of diagnostic technologies, 2) support of the applied research necessary for the development of these technologies, 3) field testing of candidate technologies, and 4) promotion of the transfer of these technologies through the development of instructional materials, dissemination of information and provision of technical assistance.

3. The agreement(s) which may be negotiated and executed by the officer(s) to whom such authority is delegated in accordance with A.I.D. regulations and Delegations of Authority shall be subject to the following terms and conditions, together with such other terms and conditions as A.I.D. may deem appropriate.

4. Source and Origin of Commodities, Nationality of Services

a. Commodities financed by A.I.D. under the project shall have their source and origin in the cooperating country* or the United States except as A.I.D. may otherwise agree in writing. Except for ocean shipping, the suppliers of commodities or services shall have the cooperating country or the United States as their place of nationality, except as A.I.D. may otherwise agree in writing.

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* Each country where research, training, technical, or other assistance takes place under the project shall be deemed to be a cooperating country for the purpose of permitting local cost financing of goods or services for the activity being conduction in such country.

b. Ocean shipping financed by A.I.D. under the project shall, except as A.I.D. may otherwise agree in writing, be financed only on flag vessels of the United States.

James E. Sain
Agency Director for Health
and Population

Clearances:
ST/H/CD, JErickson _____ Date 4/26
ST/H,WOglesby _____ Date 26 Apr 85
ST/H,AVanDusen _____ Date 4/26/85
GC/CP, STisa (Draft) Date 4/19/85
ST/PO, GEaton _____ Date 4/30/85

ST/H:WOglesby:SKStansfield:tns:4/8/85:2373u:X5-8934
Revised:4/24/85

April 25, 1985

ACTION MEMORANDUM FOR THE AGENCY DIRECTOR FOR HEALTH AND POPULATION

FROM: S&T/H, Ann Van Dusen Ann Van Dusen

SUBJECT: New Project -- Diagnostic Technology Development (936-5935)

Action: To authorize a new seven year project for Diagnostic Technology Development (936-5935) at an estimated total cost not to exceed $10 million.

Discussion: Proper health care for individuals and effective public health planning rely on accurate medical diagnosis. Diagnosis has two fundamental purposes: to permit specific, effective treatment of the ill patient, and to provide information needed to select disease prevention and control measures in the community.

The lesser developed countries have a burden of illness which differs dramatically from that of the developed world. In addition to the frequently debilitating or even deadly tropical diseases, people in LDCs are more susceptible to dying of the cosmopolitan diseases which affect populations the world over. Accurate assessment of the contribution that each disease makes to LDC health problems is of particular importance, since health service resources are limited. Primary health care workers and public health planners at every level require such information to allocate the health service resources to maximize impact on morbidity and mortality in their communities.

But for people in developing countries where certain diseases are endemic, the appropriate diagnosis is often not made, even among those patients who have ready access to medical care. The chronic infections of these patients, the common occurrence of multiple infections or other health problems, and the sparseness of disease specific complaints among persons inured to ill health all contribute to symptomatic ambiguity. Where little hope of adequate laboratory diagnosis exists, the patient is often subjected to a series of inappropriate treatments based on the "best guess" of the clinician.

The need for simple, inexpensive diagnostic technologies is widely recognized. In 1982, the Board on Science and Technology for International Development (BOSTID) of the National Research Council assembled an advisory panel to discuss the applications of biotechnology for LDC use. In November 1984, S&T/Health convened a group of technical advisors to discuss the state-of-the-art in tropical disease diagnostic technology in order to establish priorities for further development and applied research.

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Therefore the Office of Health proposes this project which will develop and transfer simple cost-effective diagnostic technologies for use in LDCs to permit accurate assessment of both individual and community disease burden. Activities of the project include: 1) identification of the needs and priorities for development of diagnostic technologies, 2) support of the applied research necessary for the development of these technologies, 3) field testing of candidate technologies, and 4) promotion of the transfer of these technologies through the development of instructional materials, dissemination of information and provision of technical assistance.

Existing or emerging biotechnologies will be adapted to advance A.I.D.'s health sector strategy for promoting child survival. Individual and community level diagnostic information provided by this project will provide the basis for design of treatment and control programs for three major causes of infant and child mortality: malaria, diarrheal diseases, and acute respiratory infections.

Recommendation: That you approve this project and sign the attached project authorization. A Congressional Notification has been prepared and is being cleared. This project was approved by members of the Health Sector Council on April 24, 1985.

Attachment: a/s

Clearances:
ST/H/CD:JErickson _____ Date 4/26
ST/H:WOglesby _____ Date 26 Apr 85
ST/PO, GEaton _____ Date 4/30/85

ST/H:W.Oglesby/SKStansfield:tns:4/8/85:2373u:X5-8934
Revised:4/24/85

DIAGNOSTIC TECHNOLOGY DEVELOPMENT PROJECT

DIAGNOSTIC TECHNOLOGY DEVELOPMENT PROJECT

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1. SUMMARY

The Bureau for Science and Technology proposes a new seven year $10 million project, Diagnostic Technology Development, 936-5935.

The project will develop and transfer simple cost-effective diagnostic technologies for use in LDCs which will permit accurate assessment of both individual and community disease burden. Activities of the project include: 1) identification of the needs and priorities for development of diagnostic technologies, 2) support of the applied research necessary for the development of these technologies, 3) field testing of candidate technologies, and 4) promotion of the transfer of these technologies through the development of instructional materials, dissemination of information and provision of technical assistance.

Existing or emerging biotechnologies will be adapted to advance AID's health sector strategy for promoting child survival. Individual and community level diagnostic information provided by this project will provide the basis for design of treatment and control programs for three major causes of infant and child mortality: 1) malaria, 2) diarrheal diseases, and 3) acute respiratory infections. These three areas for development of diagnostic strategies will function as models for applications of new biotechnologies in the treatment, prevention, and control of other LDC disease problems.

The AID project manager will have technical and administrative responsibilitiy for the project. A prime contractor will be obtained competitively to provide administrative coordination and technical support to the project. A technical advisory group will advise the project manager in establishing project priorities and policies.

2. BACKGROUND

Proper health care for individuals and effective public health planning rely on accurate medical diagnosis. Diagnosis, thus, has two fundamental functions: the individual - to permit specific effective treatment of the ill patient; and the community - to provide the information needed to select disease prevention and control measures, to evaluate community health status, and to assess the impact of interventions.

The lesser developed countries (LDCs) have a burden of illness which differs dramatically from that of the developed world. In addition to the frequently debilitating or even deadly tropical diseases, people in LDCs are more

susceptible to dying of the cosmopolitan diseases which affect populations the world over. Accurate assessment of the contribution that each disease makes to LDC health problems is of particular importance, since health service resources are limited. Primary health care workers and public health planners at every level require such information to allocate the health service resources to maximize impact on morbidity and mortality in their communities.

Diagnosis of tropical diseases in patients returning, after international travel, to developed countries is often a challenge. The alert clinician, however, can usually identify the offending infection based on travel history and the clearly identified complaints of a patient unaccustomed to ill health, whose symptoms are likely to represent recent rather than chronic infection. In addition, laboratory diagnosis in the developed countries is easily arranged in reference laboratories eager to diagnose such exotica with their expensive reagents and sophisticated laboratory equipment.

But for the persons in developing countries where those infections are endemic, the appropriate diagnosis is often not made, even among those patients who have ready access to medical care. The chronic infections of these patients, the common occurrence of multiple infections or other health problems, and the sparseness of disease-specific complaints among persons inured to ill health all contribute to symptomatic ambiguity. Where little hope of adequate laboratory diagnosis exists due to the lack of trained manpower and the high cost and logistical problems of existing diagnostic technologies, the patient is often subjected to a series of inappropriate treatments based on the "best guess" of the clinician.

The "best guess" diagnosis is selected from the assumed spectrum of regional disease problems. In turn, those local disease surveillance data are most often based on crude or inaccurate diagnostic data obtained at the primary health care level and collated by public health planners. Therefore individual treatment programs, health services planning, and disease prevention or eradication strategies are often inappropriately designed, resulting in the waste of scarce resources. Such improper treatment of disease also contributes to the alarming increase in resistance to the limited armamentarium of antibacterial, antimalarial and antihelminthic drugs.

The burgeoning of biotechnology has provided applications to diagnostics that may be selectively "harvested" for such uses in LDCs. Sophisticated diagnostic technologies have long been available for the developed world, and dramatic advances in rapid diagnosis are made with increasing frequency as we exploit the newly available methods such as

monoclonal antibody and recombinant DNA (deoxyribonucleic acid) technologies. However, scientists and manufacturers in the developed world have created these products for their own markets. Health care priorities of the affluent nations also encourage the development of diagnostic techniques which may be extremely costly, whereas minimal additional applied research with an eye for LDC needs may provide cost-effective and marketable adaptations of new techniques.

Even when appropriate diagnostic technologies have been developed, researchers often lack contacts with LDC health care providers to promote field testing of diagnostic tests which show promise. Manufacturers and health care providers may correctly shun candidate tests that have not been field-proven with documented sensitivity, specificity, and reproducibility. This project is designed to address these problems.

Traditional laboratory diagnostic technologies involve: 1) direct examination of specimens or cultures of blood, stool, urine, sputum, or tissue biopsy using simple equipment (e.g., the light microscope) and reagents or, 2) immunologic techniques, including the detection of antibodies produced by the patient in response to an infection, and the use of antibodies (usually produced in animals) as reagents to detect the pathogen or other evidence of infection in specimens from the patient. These latter methods often have significant advantages over direct examination methods but usually require specialized equipment or reagents. The direct techniques, though often inexpensive, generally require specially trained personnel, are time-consuming, and frequently fail to detect evidence of infection.

Newer diagnostic methods which offer promise for LDC use include those using monoclonal antibody and DNA or RNA (ribonucleic acid) hybridization technologies. These methods provide hope of producing rapid, simple, highly accurate and inexpensive tests which can be performed with crude specimens (such as small quantities of unprepared stool) under field conditions.

Monoclonal antibodies are produced using hybridoma technology, which was invented in the mid-1970's. Short lived antibody-secreting cells derive immortality from their fusion with tumor cells (called myelomas). The resulting hybridomas, produced in mice immunized with the chosen antigen, can be screened to identify and produce clones derived from a single cell which produce the desired antibody. The selection of a colony of cells, all of which produce identical antibody, allows relatively inexpensive manufacturing of highly specific reagent materials.

Technologies employing monoclonal antibodies are being exploited to develop diagnostic tests for malaria (1,2),

several diarrheal diseases (3,4), and acute respiratory infections (5,6). These tests show promise of high sensitivity and specificity, but require additional applied research to further field test or adapt them to use materials and indicator systems which are inexpensive, reliable under field conditions, and require no sophisticated equipment for reading.

Developments in DNA hybridization technology provide an emerging opportunity to use the actual DNA or RNA of an organism as a "probe" to identify evidence of infections. DNA can be isolated from an organism or virus, cloned to produce quantities of the genetic material, separated from the double helix to a single-stranded state, then used to test for matching material in a clinical specimen. If the suspected organism or virus is present, the DNA from the specimen will hybridize with the probe DNA.

The ability of the probe DNA to match and hybridize with the DNA in the specimen is classically indicated by the use of radioactive DNA probes which permit measurement of their ability to "stick to" the specimen. Such methods require the ability to measure radioactivity using sophisticated equipment. However several researchers have used enzymes coupled to the DNA to permit use of enzyme-induced color changes as an indicator of hybridization (7). Such alternative indicator systems may permit adaptation of this technology to LDC settings.

DNA probes have been explored for the diagnosis of malaria (8), diarrheal diseases (9-12), and a few acute respiratory infections (13), although more work is needed to link these probes to a visually readable indicator system. Another promising area of research is the use of RNA as a probe, since the higher concentration of that nucleic acid in specimens may provide diagnostic tests with greater sensitivity (14).

A major advantage of DNA probes is their high specificity, such that individual species of malaria parasites may be distinguished (15), for example, without the need for an experienced microscopist. The test may be developed to be simple and relatively inexpensive, and many specimens can be collected, stored and run in large batches if necessary for large surveys (10). Additional work must be done, however, to provide such field-practical tests which are sensitive enough to detect low levels of infection in clinical specimens.

Both probe and monoclonal antibody technologies might be combined with visually readable, inexpensive indicator technologies such as the Indium slide tests, which have been used for detection of both antigens (16) and antibodies (17).

The need for simple, inexpensive diagnostic technologies is widely recognized. The Office of the Science Advisor supports research efforts in diagnostic technology development through its program in Science and Technology Cooperation (PSTE) project (see attachment 1) and through the AID-supported Board on Science and Technology for International Development (BOSTID) grants program in the area of acute respiratory investigations which will receive careful scrutiny in identification of promising candidate technologies for further development and/or field testing. Investigators in both of these programs who have developed promising technologies will be involved, as feasible, in further work adapting or field-testing these diagnostic tests.

In 1982, (BOSTID) assembled an advisory panel to discuss the applications of biotechnology for LDC use (18). Aware of S&T/Health's concerns and LDC needs for diagnostic technologies, BOSTID now plans a meeting to discuss the use and development of diagnostics for infectious diseases of importance in LDC's (see Attachment 2). And in November, 1984, S&T/Health convened a group of technical advisors to discuss the "state of the art" in tropical disease diagnostic technology in order to establish priorities for further development and applied research. This project will address the three highest priorities identified for diagnostic test development: 1) malaria, 2) diarrheal disease, and 3) acute respiratory infections.

3. PROJECT DESCRIPTION

3.1 Goal

To improve the health status of LDC populations.

3.2 Purpose

To develop and transfer simple, cost-effective diagnostic technologies for use in LDCs which will permit accurate assessment of both individual and community disease burden.

3.3 Activities

The project will identify needs and priorities for diagnostic technology development, and support the applied research necessary for the development and field testing of these technologies. It will promote the transfer of these technologies through the development of training materials for their use, dissemination of information and provision of technical assistance.

Many tropical disease problems which plague the LDCs require improved diagnostic capabilities before treatment and

prevention programs can be appropriately designed. However, to provide a model for the adaptation of newer biotechnologies for use in diagnostics, three major disease problems have been selected. Within this project, efforts to develop and transfer diagnostic technologies will be focused on: 1) malaria, 2) diarrheal diseases, and 3) acute respiratory infections. The selection of these three disease problems reflects AID's health sector strategy in promoting the control of these major causes of infant and child mortality. Although the limitation in available resources requires the identification of three target disease problems, additional resources may be available, for example through regional bureaus and missions, to adapt diagnostic technologies for other diesease problems.

3.3.1 Applied Research Activities

Research activities within the project will be of three categories: 1) laboratory-based technology development research, 2) field assessment research, and 3) operations research.

3.3.1.1 Technology Development

A number of diagnostic technologies are ready for field testing. Many promising methods will, however, require adaptation for LDC use. While no basic research on diagnostic methodologies is planned under this project, specific product-oriented research activities will be carried out through subcontracts to adapt promising technologies to LDC needs and capabilities. Several unsolicited proposals and descriptions of ongoing research have already been forwarded to S&T/Health, documenting the large numbers of innovative diagnostic technologies which are available for adaptation and transfer to LDC's.

3.3.1.1.1 Malaria Diagnostic Technology Development

Malaria remains one of the greatest public health problems in the world. Hundreds of millions of people live in areas where malaria is endemic. More than 300 million cases occur per year and over one million infants and young children die each year in tropical Africa alone (19). Before the emergence of drug resistance, safe and effective standardized antimalarial regimens were available, permiting presumptive treatment of suspected cases based on clinical diagnosis alone. But as resistant malaria strains require treatment regimens which may be more risky or expensive, the need for specific diagnosis becomes more acute. Accurate identification of malaria strains will also be essential when the newly available candidate vaccines for malaria are field tested in order to distinguish vaccine-failures and successes.

The diagnosis of malaria based on clinical examination alone is difficult, particularly in endemic areas where patients are partially immune due to previous infections. Detection of antibodies, which persist after cure, is not sufficient for diagnosis, since the antibodies may indicate either active or previous infection. Diagnosis, therefore, depends on the detection of parasites in the blood and is conventionally established by microscopic examination of a stained blood smear. The process requires highly trained technicians, however, and is time consuming, so that it is not feasible for large surveys.

Promising technologies for malaria diagnosis include an enzyme-linked immunosorbent assay (ELISA) using monoclonal antibodies (2,20), and a DNA hybridization test (8,15). This project will finance the further work which is required to improve the sensitivity of these methods, and the selection of indicator systems which are simple, use heat stable reagents and are visually readable. Quicker and easier diagnostic tests for malaria will greatly facilitate field-testing of the candidate malaria vaccines and reduce the emergence of drug resistance and the costs of care by avoiding the inappropriate use of antimalarial drugs.

3.3.1.1.2 Diarrheal Disease Diagnostic Technology Development

Acute diarrheal illnesses are the leading cause of death in many developing countries, with the great majority of the 4.6 million deaths per year among infants and children (21). Children under five experience an average of four to eight diarrheal episodes per year (22). In addition to the mortality attributable directly to acute diarrheas, those who survive recurrent episodes are left more malnourished and weakened, at increased risk of other mortal illnesses.

Only 10-15 years ago the etiologies of diarrhea were so poorly understood that this major cause of mortality in LDCs was known as "acute undifferentiated diarrhea of the tropics." Today, recognized enteropathogens account for up to 80% of acute diarrheal episodes in those few areas where such epidemiologic studies have been completed. It is uncertain, however, whether the remainder are caused by as yet unidentified pathogens or by known agents which are undetected due to the insensitivity of our diagnostic tests.

As is evident in enumerating the causes of acute diarrheal disease in LDC's, the etiologic agent may be any one of over 20 major bacteria, viruses and parasites which infest the intestinal tract. An important advance in the treatment of acute diarrheal illness was achieved with the development of oral rehydration therapy (ORT) in the late 1960's. Although ORT is appropriate for any diarrheal disease associated with volume depletion, it is simply a non-specific, supportive measure. Some of diarrheal illness is caused by infections

which respond to antimicrobial drug treatment. However, antibiotics are often inappropriately used to treat viral or secretory diarrheas which are unaffected by expensive antibiotics. Since simple, sensitive techniques for identifying the major etiologic agents are not widely available, the causes of diarrhea are known in only a very few geographic areas. Appropriate prevention and control program for this major cause of infant and child mortality will be feasible only when the epidemiology of diarrheas can be sorted out through the availability of field-tested diagnostic technologies.

Viruses are increasingly recognized as important agents of gastroenteritis. Rotaviruses and Norwalk agents are of principal concern, although several other types of viruses are also found in fecal specimens of patients with diarrhea. Conventional cell culture procedures and electron microscopy are not feasible diagnostic techniques for general LDC use. An ELISA "kit" for diagnosis of rotavirus diarrheas has been developed and is currently in use. This project will finance applied research on a second generation test using monoclonal antibodies which could provide significant advantages in sensitivity and specificity. DNA hybridization probes have given good preliminary results (9), although more field evaluation is required.

Similar promising technologies may be readily adaptable for use in diagnosis of bacterial causes of diarrhea. Strain identification for Escherichia coli (E. coli) has become important in recent years as we have come to understand the different mechanisms by which those strains cause illness. DNA hybridization techniques have shown preliminary promise for field use in identification of the enterotoxigenic E. coli (1000 times more sensitive than conventional assays (10)) and Salmonella bacteria (12). More work is needed to promote identification of Campylobacteria and Vibrio species (including cholera) as there is an emerging appreciation of their importance as causes of acute diarrheas (23). The project will seek to develop a panel of tests including each major agent which could identify the "culprit" in each case using a single stool sample. Such simple and comprehensive diagnosis of diarrheal disease would provide the basis for rational design of treatment and control measures for this major cause of infant and child mortality in LDCs.

3.3.1.1.3 Acute Respiratory Disease Diagnostic Technology Development

It is estimated that 12% of all deaths in LDCs are attributable to acute respiratory infections (24). One half of all malnourished children will experience an episode of pneumonia in any given year (25). Mortality rates among patients hospitalized for pneumonia in Africa range from 17% in adults to nearly 50% in children (26,27). Many viruses, bacteria, fungi and parasites may cause respiratory

infectons, such that the diagnosis can be complex. Often, the results of a diagnostic test, such as a culture or paired blood tests, are not available until after the infection has passed.

Fortunately, much diagnostic information can be obtained from clinical symptoms to develop clinical algorithms or decision trees for use in primary health care. In this way, the drawbacks of limited laboratory capabilities can be minimized. However, in many cases the etiologic agent still needs to be identified. The inappropriate use of antibiotics in viral infections is costly in developed as well as developing countries, and contributes to emerging resistance of the bacteria to our antibiotic armamentarium. Specific diagnosis is necessary to plan, implement and evaluate interventions against both epidemic and ongoing or endemic infection.

Simple microscopic examination of stained sputum specimens is useful, though rarely sufficient for diagnosis. Conventional culture and isolation of the pathogen and serologic diagnosis (requiring examination of two specimens, generally two weeks apart) remain logistically difficult in LDCs and will only produce confirmation of a diagnosis after the infection has either resolved or claimed the host. Such information may be used "post hoc" in epidemiologic studies but is of no value for individual patient care.

Newer technologies are being tapped for use in diagnosis of acute respiratory infections. Detection of two important pathogens, Streptococcus pneumoniae and Hemophilus influenzae, is possible using coagglutination; the latex agglutination and ELISA methods hold additional promise for field use but require further study. Respiratory syncytial virus is an important infection among infants and children which can be diagnosed within hours using an immunofluorescent assay (IFA) (28). This technique, however, requires costly fluorescent microscopes and highly trained technicians and is thus inappropriate for widespread use in LDCs. The method might be adapted however using an enzyme indicator system, for example, to improve our diagnostic capabilities. Most other viruses, including parainfluenza, influenza, adenoviruses, rhinoviruses and coronaviruses, require tissue culture isolation for identification which makes diagnosis too difficult and time consuming for routine clinical use. DNA or RNA hybridization techniques may be explored, but since more basic research is required, project activity in this area is not anticipated to begin until the third year.

3.3.1.2 Field Assessment

Existing technologies as well as those developed within this project require careful testing and documentation of their reliability under field conditions before they can be

adopted for routine use. Many research institutions which have developed or are developing diagnostic tests lack the necessary contacts with LDC public health planners and health care providers needed to promote field testing of their tests. The field assessment component of the project will address this problem.

Field assessment of diagnostic technologies will be coordinated with international agencies including WHO and UNICEF, regional health organizations in West and Central Africa, and the national research institutes in Southeast Asia and the Middle East. Regional bureau or USAID mission concerns or requests for technical assistance and epidemiologic assessment may provide opportunities for field assessment of diagnostic technologies. Collaboration with WHO, Centers for Disease Control or other agencies in epidemic investigations may provide opportunities for field evaluation of diagnostic tests. Field activities which complement WHO's CDD and TDR programs and the Great Neglected Diseases Program of the Rockefeller Foundation will be given special attention. Wherever possible, joint programs, shared financing, and "piggy-backing" on existing field program will be pursued.

Field assessment of technologies developed for malaria diagnosis will be coordinated to complement the activities of AIDs malaria vaccine development project. As sites are selected for testing of the candidate malaria vaccines, the need will emerge for careful documentation of parasite dynamics prior to and following vaccinations. Concerned personnel have already been tentatively identified in Asia, Latin America, and Africa who may act as investigators or collaborators in field assessment of malaria diagnostics. Funding from the malaria vaccine development project, local missions and/or regional bureaus will be sought for some of these activities.

Evaluation of diagnostic tests for diarrheal diseases will be coordinated with AIDs Applied Diarrheal Disease Research project. The development of research capabilities in LDC institutions provided for in that project contribute to our efforts to test improved rapid diagnostic technologies.

3.3.1.3 Operations Research

The availability of these more specific diagnostic tests will provide primary health care workers and public health planners with information to improve health service delivery systems. To assure maximum beneficial use of data from these tests and to evaluate the impact of project activities, the project will incorporate an operations research component. Just as the proposed diagnostic tests have been selected based on their expected importance for treatment and prevention strategies, identification of technologies for transfer must be made based on their

observed utility in treatment and public health planning.

Operations research consultation will be obtained by the prime contractor to address questions such as the follwoing:

- In the face of limited health care resources, how can we select for development those diagnostic technologies which will prove most useful for health care planning?

- At what level in the health care system should each of these diagnostic strategies be implemented for maximal cost-effectiveness?

- What "weight" should each criterion receive in selecting the ideal diagnostic tests for development (e.g., should sensitivity of a test be sacrificed, in part, to achieve some increased specificity? Or, will a small increase in the difficulty of execution render a test useless where training is limited?)

- In areas where diagnostic technologies promoted by the project have been implemented, what has been the impact on cost and quality of care, or decreased morbidity and mortality?

- Can we identify "branch points" in the decision trees of primary health care and public health planning which inform us about the most critical needs for diagnostic technology development?

- Which diagnostic technologies are likely to offer adequate opportunities for profit to LDC or developed country-based industries to enable these technologies to be incorporated in the delivery system as are drugs, medical equipment and other essential purchases.

- Can we project the potential impact of accurate diagnosis on the patterns of drug resistance through modelling techniques?

3.3.2 Training Material Developmnet

The development of training materials for the technologies developed or field-tested within the project will be essential for effective transfer of some of these diagnostic strategies to LDCs. Involvement of laboratory-based scientists as well as field investigators in the preparation of training materials will be necessary to ensure that host country technicians have the capability to use these diagnostic tests. Awareness of the sensitivity and specificity limitations of a diagnostic test and the susceptibility of its reagents to contamination or deterioration are essential if LDC technicians are to use these technologies efficiently. Expertise in training materials development will be incorporated in the technical

advisory group so that such needs may be considered from the outset. Subcontracts for development of training materials may be solicited separately as necessary, although efforts will be made to incorporate training development into technology development contracts as institutional capabilities permit.

3.3.3 Information, Education and Communication (IE&C)

LDC public health planners and primary care providers involved in field testing these technologies will be trained in the use of these new diagnostic tests through the information dissemination, education and communication component of this project. Training materials developed under contracts with developers of new diagnostics will be used in training courses, symposia, and/or workshops funded under this component of the project. It is anticipated that these "pilot" training symposia or workshops will occur in areas selected for field testing of the diagnostic tests. Subsequent regional training efforts in the use of these new technologies can be conducted under funding by USAID missions, with the possible provision of short-term consultation under the technical assistance activities of the project as outlined below.

Contractors funded for research and development, field testing, training material development or operations research activities will be kept informed of activities in other project components. Updates on important project accomplishments will also be circulated to AID regional bureaus and missions so that relevant personnel may be made aware of available technologies and program support, particularly in the event of epidemics or other disasters requiring rapid investigation or disease surveillance.

Special efforts will be made to involve the private sector, both U.S. and LDC, in the transfer of this technologies to LDC's. Modalities for enhancing commercial incentives in these adaptations of biotechnology will be explored though inclusion of appropriate personnel in the technical advisory group. Preference will be given to those technologies which show promise of providing a profit motive for ongoing production, especially if that production is feasible within LDCs. In addition, institutions such as ministries of health and universities will be involved as much as possible in developing, field-testing, adapting and sustaining the use of these technologies. Technical assistance will be provided, as outlined below, to assist LDC institutions in planning the implementation and evaluation of these new diagnostic technologies, and to assess the feasibility of development of indigenous manufacturing capabilities so that these activities will be sustained after the termination of the project.

3.3.4 Technical Assistance

Included in project activities is the provision of technical assistance upon requests by subcontractors, host country ministries of health, private or public agencies, organizations and programs. Technical assistance will be available: 1) to address technical problems in technology development, 2) to address the operations research issues outlined above (section 3.3.1.3), 3) to assess local needs for diagnostic technologies, 4) to assist in training technical personnel, and 5) to support indigenous commercial enterprises in assessing the feasibility of development of manufacturing capabilities.

3.3.5. Other Activities

In the implementation of the project, needs may arise for activities which have not been specified under research, training, information dissemination or technical assistance categories. When consistent with the project purpose, the project manager may approve the use of project resources to support other activities such as, conferences or symposia, travel for key technical or administrative personnel, and data analysis.

4. IMPLEMENTATION

4.1. AID Management

The AID project manager within the Communicable Disease Division, Office of Health (S&T/H/CD) will have technical and administrative responsibility for the project. The project manager will insure that project activities are consistent with the goal, purpose, and implementation plan outlined in this project paper. Activities conducted under the project including subcontracts, operations research, conferences or symposia, information dissemination activities, training, consultations and travel will be approved by the project manager.

4.2 Prime Contractor

4.2.1 Prime Contractor Activities

A prime contractor will be obtained competitively to provide administrative coordination and technical support to the project. The prime contractor will have capabilities to coordinate the research, training and information dissemination activities, and provide or obtain technical assistance as appropriate. The prime contractor will also provide administrative assistance including distribution of communications among the network of subcontractors, coordination of arrangements for conferences, training seminars, or international travel, shipping of reagents or

supplies and production of training materials as required. A roster of consultants possessing technical expertise in areas relevant to project activities will be maintained. The prime contractor will act as a project clearing house for information regarding the state of the art in diagnostic technology development.

Applied research in technology development will be performed by subcontractors. Proposals for applied research will be reviewed by an appropriate subgroup of the Technical Advisory Group. In the first two years of project activity, it is anticipated that small subcontracts will be initiated in malaria and diarrheal disease technology development. More significant funding of research in these areas and the initiation of research in acute respiratory disease diagnosis will begin in the third year.

Field assessment of existing diagnostic technology will begin in the first year of the project with significant increases in later years to field test the products of the project's applied research. Field assessments will be implemented by the prime contractor either through consultants hired for the purpose, or through subcontracts. In all cases of field assessments, the prime contractor shall be responsible for the creation and uniform application of a standard protocol to assure comparability of data.

The other project activities (operations research, training materials development, information, education and communications activities, technical assistance and other activities) shall be performed by the contractor through the use of its own staff or through subcontracts. In each case, the selection of implementation method shall be subject to the prior approval of AID.

4.2.2. Prime Contractor Staff

The staff must have adequate knowledge of and contacts in the field to coordinate project activities outlined above, and to identify potential subcontractors and consultants to provide technical assistance. The contractor staff will provide all necessary logistical and administrative support required to carry out the project activities outlined above.

4.2.3 Prime Contractor Facilities

The prime contractor will provide office space appropriate for the staff as listed above, and any required space for visiting contractors and consultants. The prime contractor should have access to a small conference room and will provide photocopy and data processing equipment. The expenditure of project funds will not be authorized for construction or renovation of facilities.

4.3 Technical Advisory Group

To assist in the establishment and ranking of priorities for project activities a technical advisory group will be selected. The group will be chaired by the project manager and be composed of approximately twelve members who will meet annually (or additionally as necessary), and who possess technical expertise in areas such as:

- Malaria diagnostics
- Diarrheal diseases diagnostics
- Acute respiratory illness diagnostics
- Medical anthropology
- Biotechnology and commercial incentives
- Operations research
- Medical technology education
- DNA probes
- Monoclonal antibody technology
- Rapid diagnostic indicator systems

Additional advisory group members may be invited on an ad hoc basis when special problems or issues need to be addressed in the course of the project.

The prime contractor will provide all necessary administrative support for the technical advisory group. The group will advise the project manager in establishing priorities for the development and testing of diagnostic technologies. Subgroups of the TAG selected by the project manager may also be requested to review proposals from subcontractors either by mail, or at special meetings. Project priorities and policies recommended by the TAG will be translated into project activities by the prime contractor with the concurrence of the AID project manager. TAG members will be reimbursed for travel and per diem costs, but will not receive salaries.

4.4 Timetable

	TASK	DATE
1.	Project authorization	April 1985
2.	Synopsis published in CBD	April 1985
3.	Congressional notification	April 1985
4.	PIO/T	May 1985
5.	RFP announced in CBD	May 1985
6.	Award of prime contract	August 1985
7.	Prime contract operations begin	August 1985

8.	First meeting of TAG, TAG report	September 1985
9.	Development of annual work plan	September 1985
10.	Award of first subcontracts for technology development	October 1985
11.	Award of first subcontracts for technology field-testing	November 1985
12.	First field tests with pilot use of training materials	February 1986
13.	Quarterly reports from prime contractor to USAID	Jan, April, July Oct, (beg. Jan 86)
14.	External evaluations	Oct, 1988, 1990

4.5 Budget

The total life of project funding will be $10 million over seven years. The total project resources are tentatively allocated among expenditures as follows:

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	TOTALS
pplied Research								
Technology Dev.	$250	$275	$ 750	$1,200	$1,000	$ 450	$ 200	$ 4,12
Field Assess.	100	125	225	300	450	350	275	1,82
Opns. Res.			25	50	50	50	50	22
raining Materials Dev.			25	25	100	50	50	25
echnical Assist.	25	50	100	125	175	175	125	77
ontractor, Opns, & TAG Support	175	225	300	375	400	300	250	2,02
valuation			25			50		7
ontingency	50	50	100	150	175	100	75	70
OTALS	$600	$725	$1,550	$2,225	$2,350	$1,525	$1,025	$10,00

4.6 Reports

The prime contractor shall submit reports as follows:

1. Two reports will be submitted annually consisting of a semi-annual interim activity report and one annual progress report (submitted 12 months after the project commences and annually thereafter). All reports shall be submitted to the AID project manager in six copies covering ongoing and completed activities as well as plans for the next six months. The reports should include, but not be limited to a description of activities, summary of results and accomplishments and problems in the areas of program development and execution.

2. All financial reports and vouchers for payment and reporting of expenditures will conform to standard AID regulations and procedures.

4.7 Evaluation

The project will be closely monitored on a continuing basis by the project manager with the assistance of the technical staff of the Office of Health. There will be annual project reviews. Major external evaluations are anticipated at the end of the third year and again at the end of the sixth year. AID staff and outside experts will make detailed assessments of project organization and development, project management, project outputs, and will make recommendations for future activities The results of the sixth year evaluation will be used to make decisions on project continuation.

4.8 Conditions and Covenants

Agreements which may be negotiated under this project and executed by the officer(s) to whom such authority is delegated, in accordance with AID regulations and Delegations of Authority, shall be subject to the following terms and conditions together with such other terms and conditions as AID may deem appropriate:

Source and Origin of Goods and Services

Each country where research, training, technical or other assistance takes place under this project shall be deemed to be a cooperating country for the purpose of permitting local cost financing. The sum of all purchase orders, contracts and subagreements for goods and services under each contract or subagreement in a cooperating country may be procured in the special free world category (Code 935) up to $750,000 for the purpose of permitting local cost financing.

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AID 1020-20 (1-78)

PROJECT DESIGN SUMMARY
LOGICAL FRAMEWORK

Life of Project:
From FY 85 to FY 91
Total U.S. Funding 10,000
Date Prepared: 1 April, 1985

Project Title & Number: DIAGNOSTIC TECHNOLOGY DEVELOPMENT PROJECT 936-5935

NARRATIVE SUMMARY	OBJECTIVELY VERIFIABLE INDICATORS	MEANS OF VERIFICATION	IMPORTANT ASSUMPTIONS
Program or Sector Goal: The broader objective to which this project contributes: To improve the health status of populations in developing countries	**Measures of Goal Achievement:** Reduction in disease-specific morbidity and disease-specific mortality.	1) Statistics (disease incidence, morbidity, mortality) from ministries of health 2) Information from WHO annual reports and statistics 3) AID or other project statistics	**Assumptions for achieving goal targets:** Impact of this project on morbidity and mortality rates can be distinguished from that of other projects and other variables.
Project Purpose: To develop simple, inexpensive diagnostic technologies for use at the primary health care and community level.	**Conditions that will indicate purpose has been achieved: End of project status.** Improved diagnostic tests for malaria, diarrheal diseases and acute respiratory illnesses which are field tested and in use in developing countries	1) Data from ministries of health 2) Reports from WHO and PAHO 3) Project reports and evaluation	**Assumptions for achieving purpose:** LDC primary health care systems can and will make the short-term investment in diagnostic kits and the attendant training necessary to achieve longer-run efficiencies and economies
Outputs: 1) Diagnostic "kits" for malaria, diarrheal diseases and acute respiratory illnesses which are field proven, are accompanied by instructional materials, and are feasible and profitable for production and marketing in developing countries. 2) Technical assistance 3) Information, education and communication to LDCs.	**Magnitude of Outputs:** 1) The selected technologies adapted for diagnosis of each of the three target disease problems 2) Advise 10-15 LDCs in adapting diagnostic technologies 3) Dissemination of information regarding use of technologies among AID-assisted countries	1) Subcontractor reports 2) Market comparisons 3) WHO, PAHO and industry reports 4) USAID reports 5) Project evaluations	**Assumptions for achieving outputs:** Severe field conditions and interventions of multiple diseases will not be insurmountable problems.
Inputs: Administratively support and $10 million operational funding for diagnostic technology development activities.	**Implementation Target (Type and Quantity)** 1) Management contract 2) Applied research subcontract a. malaria diagnostics development b. diarrheal disease diagnostics c. acute respiratory illness diagnostics 3) Field assessment subcontract 4) Technical assistance	1) Prime contractor's records 2) Mission reports and surveys 3) Reports from host country ministries 4) Project reports and evaluation	**Assumptions for providing inputs:** Research organizations' current developed country orientation can be redirected to LDC conditions and needs

Attachment No. 1

Office of the Science Advisor
Program in Science and Technology Cooperation
Biotechnology/Immunology Module
Selected Proposals with Potential Relevance to
Diagnostic Technology Development Project

Title	Investigator	Institution
Immunization against Trypanosomiasis: Potential of a Non-glycoprotein Surface Component Approach	Stek, M.	USUHS
Pathogenesis of Viral Diarrhea (A toxin-recognition-like approach)	Holmes, K.V.	USUHS
Purification of Mycobacterial Antigens for Potential Use in Seriological Diagnossis of Tuberculosis	Johnson, A.H.	Eastern Vir. Med.
The Production of Antigens of Onchocerca volvulus by Recombinant Microbiology	Levy D.	JHU
Development of Monoclonal Antibodies Against Trypanosoma cruzi	Azocar, J.	IVIC
ELISA Diagnosis of Tuberculosis in Bolivia	Daniel, T.	C.W. Reserve U.
Onchocerciasis in United Republic of Cameroon: Development of ELISA for Immunodiagnosis	Levy, D.A.	JHU
Application of New Tech. in Biochem. & Molecular Biol. for Studies on Parasite/Vector Relationships in Leishmaniasis	Greenblatt, C.L.	Hebrew
Detection of Snails Infected With Schistosoma mansoni By the Use of Molecular Probes	Hamburger, J.	Hebrew

The Application of Microbial Genetics to the Study of Transmission and Pathogenesis of Infantile Diarrhoea in Rangoon	Tin Aye, D.	Dep. Med. Res. (Burma)
Speciation of Infective Larvae of Filarial Nematodes & Identification of Species-Specific Antigens of Brugia malayi	Piessens, W.	Harvard
Production of Monoclonal Antibodies to Salmonellae that Cause Enteric Fever (5.227)		Mahidol U. (Thailand)
Rapid Diagnosis of Human Leishmaniasis: Use of Biotinylated K-DNA Probes in the Detection of New World Leishmania sp. (5.203)		U. Peruana Cayetano Heredia, Lima, Peru (in collaboration w/ Harvard)
Immunochemical Characterization of Immunogenic Proteins of Onchocerca volvulus, Adult Worms, Microfilariae, and Infective Larvae (5.189)		U. of Sierra Leone, Freetown, Sierra Leone West Africa, in collaboration w/Case Western U., Ohio, Cleveland.

ST/H/CD:SKStanfield:tns:4/12/85:1214t

Attachment No. 2

NATIONAL RESEARCH COUNCIL

OFFICE OF INTERNATIONAL AFFAIRS

2101 Constitution Avenue Washington, D.C. 20418 USA

BOARD ON SCIENCE AND TECHNOLOGY
FOR INTERNATIONAL DEVELOPMENT
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TWX#:710-822-9589 OR RCA#:248664 NASW UR

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JOSEPH HENRY BUILDING
21ST STREET AND
PENNSYLVANIA AVENUE, N.W.
WASHINGTON, D.C.

April 8, 1985

MEMORANDUM

To: Participants at the Meeting on Diagnostics for Infectious Diseases of Importance in Developing Countries

From: Heather Miller, Staff Associate HM

The Board on Science and Technology for International Development in conjunction with the Institute of Medicine of the National Academy of Sciences will be convening a meeting on May 15 and 16 in Washington, D.C. to explore issues relevant to the use and development of diagnostic tests for infectious diseases of importance in less developed countries (LDCs). The range of topics to be discussed at this meeting is necessarily large. We anticipate that the findings of these sessions will assist the Academy in defining possible further initiatives. We would therefore like to focus on the identification of important factors and processes which need to be considered in the development and use of diagnostics for LDCs. We cordially invite you to participate in this meeting.

Health resources in developing countries are severely constrained so that any diagnostic test must contribute to better health by enabling more appropriate treatment to be provided or through facilitating the design of more effective prevention strategies. Shortages of funds and trained manpower, or lack of access to sophisticated laboratory facilities require tests to be inexpensive and simple to administer and interpret. Many new diagnostic tests are being marketed or developed for use in the U.S. or other industrialized societies. This meeting will focus on the needs of LDCs for diagnostic tests and the development of tests likely to meet those needs.

We would like to look at the following issues pertaining to the use and development of diagnostics for LDCs during the course of this meeting:

* For what specific situations would diagnostic techniques improve health (a) through treatment, (b) through prevention programs?

* How can we estimate the potential benefits and set short and long term priorities?

* What is the state-of-the-art for diagnostic tests for viral, bacterial and parasitic diseases?

* What factors are important in considering modification of current tests or development of new tests for LDCs use?

* Which tests currently in use in MDCs have the most promise for use in LDCs?

* What are the promising new technologies which migh prove useful in the future development of new diagnostics?

* How should tests which would be most useful for differential diagnoses be selected for large scale application?

* What are the incentives and disincentives for R&D in the U.S.A. for diagnostics to be used in LDCs and how can these be managed better?

* What information is needed in LDCs for selection and use of infectious disease diagnostics and how can this information be made more accessible?

* What information is needed by U.S. investigators involved in R&D for development of tests for use in LDCs?

* What criteria can be used to set priorities for development of tests for LDC use?

* How should specifications for these tests be established?

The format of this meeting will be a series of informal panel discussions. We have tried to select panel members from the range of interests and fields involved in the research, development and use of diagnostic tests for infectious diseases. Due to limited resources, including space, this will be a small meeting of approximately 30 people. All participants are encouraged to contribute to each session. A summary report will be prepared that identifies the major topics discussed and which describes pertinent criteria for diagnostic test applications in developing countries.

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Enclosed you will find a copy of a tentative agenda with a list of anticipated participants. Panel leaders and members may wish to discuss the presentations with each other before the meeting. In addition, panel members will receive a list of questions or topics which we feel would be of interest or helpful in discussions of the substantive issues of that panel. These are suggestions and are in no way intended to constrain or limit the panel.

I look forward to meeting with you on May 15 and 16. In the mean time, if you have any questions don't hesitate to call me at (202)-334-2646.