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Global Tuberculosis Programme

The Tuberculosis Diagnostics Initiative

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industry to build upon existing research and technologies to produce and evaluate appropriate new diagnostic products for tuberculosis. The purpose of this summary is to review the response of the WHO Global Tuberculosis Programme's Tuberculosis to this need.

2. WHO/GTB response: The Tuberculosis Diagnostics Initiative

a. Background

During early 1996, GTB reviewed the status of efforts to develop new diagnostics for tuberculosis. This review noted that some progress in this area had been made during recent years. The basic research, including cloning of specific antigens better protein purification techniques, and the development of specific nucleic acid amplification techniques, had been largely completed. Some new diagnostics for tuberculosis were already available. Yet these new diagnostics were not appropriate for use in low income countries.

b. Formulation of the Tuberculosis Diagnostics Initiative

GTB decided that additional emphasis, in the form of a specific Tuberculosis Diagnostics Initiative was needed to speed the development of the new products with the appropriate characteristics for use in national programmes in low-income countries. GTB also concluded that the same basic research advances could, potentially, be adapted to produce practical new diagnostics for use in the field. What was needed was a means to stimulate and facilitate the diagnostics industry to adapt the available technologies to develop new diagnostics.

The Tuberculosis Diagnostics Initiative was formulated to respond directly to this need. Work was begun on this initiative during the fourth quarter of 1996.

c. The goal of the Tuberculosis Diagnostics Initiative

The WHO/GTB Tuberculosis Diagnostics Initiative seeks to work closely with interested parties [including basic and clinical researchers, with the diagnostics industry, with regulatory agencies, and with national and local health officials] to enable and facilitate the development, testing, approval, and employment of new diagnostics for tuberculosis appropriate for use in low income countries. The aim was to have these new diagnostics available for use in the field by the end of the year 2000.

3. Tuberculosis Diagnostics Initiative: strategies, activities, and accomplishments

The initial assumption that most of the basic research needed to create a new test already exists has proven to be largely correct. For example, there are currently a number of companies who are putting together tests based upon the detection of one or more specific antibodies in the serum of patients infected with *M. tuberculosis*. These tests are almost uniformly based upon the use of highly purified mycobacterial antigens that have been purified using new procedures and/or have been cloned.

1. The need for new diagnostics for tuberculosis

The diagnosis and treatment of acid-fast bacilli [AFB] microscopy positive [*i.e.* smear positive] cases of pulmonary tuberculosis forms the foundation of the World Health Organization [WHO] Global Tuberculosis Programme's Directly Observed Treatment, Short Course [DOTS] strategy to control tuberculosis. Yet it is recognized that this procedure, which was developed nearly a century ago, lacks sensitivity. As a result, cases of smear-positive [*i.e.* infectious] tuberculosis go unrecognized. Such cases constitute a significant public health concern. By definition, all tuberculosis cases that are AFB microscopy negative [*i.e.* smear-negative] are also unrecognized by this diagnostic procedure. Children with pulmonary tuberculosis, patients with extra pulmonary tuberculosis and many tuberculosis patients co-infected with HIV are often smear-negative. These cases represent less of a public health threat due to relatively low probability of transmission of the disease. Yet they remain a significant burden - both for the health care system and for the patients themselves.

There are other difficulties associated with the use of AFB microscopy for the diagnosis of pulmonary tuberculosis. In addition to questions regarding the sensitivity of AFB microscopy there are both problems with the AFB microscopy as a test for tuberculosis and important performance limitations associated with how this test is used. These problems and limitations diminish the value of this test and restrict the number of smear-positive cases of pulmonary tuberculosis actually diagnosed.

The test itself requires both functional equipment and reagents that may be difficult to obtain and distribute. WHO recommends the use of binocular microscopes for AFB microscopy. These can be a significant part of start-up costs for large tuberculosis control projects. Even glass slides can be expensive for countries that do not produce them. Where this expense becomes a consideration, slides may be re-used, a procedure that often results in scratches with subsequent increased possibilities for misdiagnosis. Finally, without proper upkeep, microscopes become unusable.

There are also problems associated with how the test is used. These include the number of patient visits to the health facility, the time required to properly prepare and analyze each sputum specimen, and with quality control. Where such problems exist, they make diagnosis of pulmonary tuberculosis by AFB microscopy a burden on both local/national health systems and national tuberculosis control programmes.

New diagnostics are needed to facilitate and improve the detection of both AFB positive and AFB negative cases of tuberculosis. This need is most acute in those low income countries where most tuberculosis is located.

Can new technologies and recent advances in tuberculosis research be combined to help develop the new products that are needed? What can WHO/GTB do to assist and facilitate this process? These are the fundamental questions that are the basis for GTB's Tuberculosis Diagnostics Initiative. This Initiative seeks to assist

The initial strategies of the Tuberculosis Diagnostics Initiative focused on the diagnostics industry. We identified both large and small companies with a current or potential interest in the development of new TB diagnostics. We next met with decision makers to stimulate interest and to identify obstacles. Finally, we identified means to assist industry to overcome the obstacles.

a. Industry survey

A survey of the diagnostics industry was initiated to determine the extent of current development efforts.

Currently, more than 50 companies have been identified with an active interest in the development of appropriate new tuberculosis diagnostics. These companies are located in 18 countries, scattered across five continents. In addition to providing an overview of efforts to develop and test new diagnostic products, the survey has proven to be especially valuable for promotion of potential alliances and partnerships.

b. Discussions with industry

Personal visits to industry decision-makers were arranged to both explain the need and to determine how WHO/GTB might use its competitive advantage to assist industry efforts to develop and evaluate the new products needed to improve the diagnosis of tuberculosis in low income countries.

c. New diagnostics: summary of needs and characteristics

We have, together with Dr. Richard O'Brien of the Division of Tuberculosis Elimination, CDC, Atlanta GA, USA, prepared a draft of a manuscript that describes the needs for and characteristics of new diagnostics for tuberculosis. In this manuscript we detail the strengths and limitations of the current tests, list the characteristics of the tests that are most needed, review the current approaches to the development of new tests, and provide some very rough estimates of the current market. The purpose of the manuscript is to assist industry decision-makers in their preparation of business plans. This manuscript has recently been sent out to a number of external reviewers including basic and clinical researchers, representatives from industry and health officials from low income countries. We have submitted it for publication and provided copies to more than 100 industry representatives.

d. Identify obstacles

The primary obstacles to the development and testing of new diagnostic products were identified during a series of personal meetings with interested parties including industry representatives, regulatory agencies, and health officials. The primary obstacle was a lack of understanding of what products were most needed and how these products would be used in the field. Other obstacles included a lack of information on the number and costs of current diagnostic procedures. Finally, the need for appropriate clinical [or field] trials was not well appreciated.

WHO/GTB organized a workshop to address some of these obstacles.

e. WHO/GTB Tuberculosis Diagnostics Workshop; product performance guidelines

The aim of the Workshop was to formulate minimum useful product performance guidelines to assist industry in the development of new diagnostic products.

Product performance guidelines that are established at "ideal" levels will not assist in this goal. Neither will guidelines that are set too low. The workshop sought to establish guidelines to assist in the development of new products that would be both practical to develop and useful in the field.

The WHO/GTB Tuberculosis Diagnostics Workshop was held on Sunday, 27 July 1997 at the Renaissance Hotel in Cleveland Ohio. This location was chosen to draw upon the experience of more than fifteen basic/clinical researchers with an interest in the development of new diagnostics for tuberculosis and five researchers and administrators from low/middle income countries where the prevalence of tuberculosis is high. These participants were already in Cleveland to attend the Annual Meeting of Case Western Reserve's Tuberculosis Research Unit. Other participants included 28 representatives from the diagnostics industry, five representatives from U.S. and European regulatory agencies, experts from mycobacteriology laboratories, and representatives from low/middle income countries with direct experience in tuberculosis control programmes.

The agenda was planned to first give participants an overview of the current status of tuberculosis diagnostics in low income countries together with a synopsis of the needs for new products. Next, a brief summary of a variety of products under development was provided by industry representatives. An overview of some regulatory considerations related to new diagnostics for tuberculosis was provided. Industry was then given an opportunity to comment on all information thus far provided. The remainder of the workshop centered on the discussions and output from four working groups, each focused on a different diagnostic need. The working group discussions were summarized and presented for discussion to all workshop participants. Finally, with industry representatives participating as observers, workshop participants finalized workshop guidelines for the new diagnostic products most needed.

f. Market estimates for new diagnostics for tuberculosis

We have only a crude idea of what the market for new tuberculosis diagnostics may be. We don't know either the total number of tests currently being administered to diagnose tuberculosis, or the cost of these tests. We do, however, have some estimates and these can help us to make some rough calculations.

For example, in Malawi, we know from an excellent and thorough study by Dr. Holger Sawert from the Global Tuberculosis Programmes, WHO Geneva that it costs \$0.31 to prepare and examine a single AFB-slide. We also know from this same study that nine suspects are examined for each case diagnosed. Thus 27 slides must be

examined at a total cost of US\$8.31 to diagnose one case. Similar figures for the cost/slide evaluated are available from other sources yet the critical information on the number of slides examined per AFB smear-positive case diagnosed [*i.e.* prevalence] is missing. Also, these figures do not include the costs of additional diagnostic tests, such as culture, chest X-ray, and antibiotic susceptibility testing that may or may not be done. We just don't know very much about how much is currently being spent for tuberculosis diagnostics. We also can only make a guess at the number of tests currently being done.

GTB decided that the effort needed to obtain accurate market information required resources beyond those available in GTB at this point for this purpose. In addition, questions were raised about the appropriateness of using WHO/GTB funds and personnel to conduct an expensive market survey that many believed to be the responsibility of industry. Finally, it was noted that even in the absence of this information, the number of companies with an interest in the development of new diagnostics for tuberculosis was increasing rapidly. It appeared that companies could be stimulated even in the absence of solid market information.

4. Future activities

a. *Specimen bank*

GTB has determined that: [1] no reliable source of well-characterized clinical specimens currently exists for this purpose and [2] the availability of such materials would markedly assist the diagnostics industry in their efforts to develop useful new products. Therefore, a meeting of consultants was held to assist GTB in the identification of steps needed to establish a specimen bank. Consultants included potential Principal Investigators [P.I.s] from sites where specimens could be collected, researchers interested in the development of new diagnostics, representatives from the diagnostics industry, and health agency officials.

A specimen bank could promote the development, evaluation, and approval of new diagnostics in a number of ways. Primarily, it would significantly improve the quality of laboratory testing of new products under development prior to costly field trials. The performance of a new product using well-characterized specimens could also assist the approval process and promote the comparison of new and existing products.

Consensus views were obtained on how GTB could assist in the creation and maintenance of a WHO/GTB Specimen Bank. Guidelines were formulated for the selection of collection sites, a draft protocol for specimen collection and characterization was formulated, and the number and types of specimens needed. These guidelines will be used to begin the process. Initial funding for specimen collection will be provided by WHO/GTB. This work is continuing. It is anticipated that specimens will become available for distribution during the 3rd quarter of 1998.

Some questions remain. The central question of how the WHO/GTB Specimen Bank will be managed remains to be finalized. Initial discussions have

identified a private company that could assist WHO in this effort. It is likely that industry will be asked to bear at least part of the costs associated with the collection and distribution of the needed specimens.

b. Field trials

The performance of any new diagnostics for tuberculosis must be demonstrated during field trials conducted at locations where such products are intended to be used. WHO will assist industry in the preparation of appropriate trial protocols and in the identification of appropriate sites for these trials.

c. Comparative studies

As new products become available, it will become necessary to provide an independent evaluation of the product performance characteristics. WHO will consider the means to accomplish such evaluations.

d. Specific recommendations

WHO will also consider making specific recommendations for the use of new diagnostics for tuberculosis within national tuberculosis control programs. These recommendations will be based upon both the performance and cost-effectiveness of these new products.

5. Tuberculosis Diagnostics Initiative: Final goals

This initiative seeks to have new diagnostics available for use in the field by the end of the year 2000. Several new products are either already available or will become available during the coming year. The focus now must be to determine which, if any, of these new products provide significant value to tuberculosis control programmes and to promote their distribution and use.