ZAMBART RESEARCH BRIEFING

TARGETS Zambart Project

TB IN THE 21ST CENTURY: THE IMPACT OF NEW DIAGNOSTIC TOOLS & APPROACHES

Tuberculosis (TB) is a global epidemic whose distribution is not uniform across the globe; populations in both Asia and Africa are the hardest hit. In order to rollback this epidemic new laboratory tests and hardware must be created for field use in an ever-changing developing world environment. In addition, sourcing local human resources to both operate and analyse the output of these emerging technologies poses a serious challenge to improving TB diagnostics.

The future of TB diagnostics lies in the ability to carry out new and innovative research to measure the impact of new diagnostic tools currently being used in the developing world, keeping in the mind the impact these tools have not only on patients but on the larger health and TB control system in place within the country. Appropriate study designs to assess impact on health outcomes, such as mortality, are urgently needed if new diagnostic tools are to change lives in resource-limited settings.

New technologies are currently being tested in the sub-Saharan African country of Zambia by the Zambia AIDS-Related TB [ZAMBART] Project.

Diagnostic tools include:

- The use of various liquid culture TB laboratory tests to examine the feasibility and accuracy of rapid TB specimen tests in a resource-limited setting;
- The use of a digital chest x-ray machine which utilizes a computer-aided diagnostic (CAD) tool for reading chest x-rays to help diagnose TB in areas where there is no radiologist;
- The use of containerized TB laboratories in large-scale TB prevalence surveys.

Each of these different technologies is aimed at streamlining and improving the patient-provider interaction and allows for more accurate and timely specimen analysis.

The need for new TB diagnostics

The burden of TB is overwhelming sub-Saharan Africa, with this region accounting for 23% of all reported cases of TB in 2005[i]. In order to curb the TB epidemic, the creation of new and practical diagnostic tools is critical. In the past, the creation of TB diagnostic tools has focused primarily on improving both the accuracy and specificity of TB laboratory tests for use in sophisticated developed world environments.

However, in the 21st century there is an increasing demand for the creation of TB diagnostic technologies that are applicable to the rigors and unpredictability of the field environment where the need and potential impact is greatest. There are also challenges surrounding the scaling up of these new diagnostic tools in a resource-limited setting with constantly changing environmental challenges. On the research side, it is important to analyse the impact of new diagnostic tools on both the patient and the existing health systems in the country.

It is also significant to acknowledge that another critical limitation in the fight against TB in the developing world is a lack of adequate human resources to operate sophisticated diagnostic equipment and laboratory tests. The large, generally lower-level educated workforce often found in the developing world makes it difficult to source and maintain talented laboratory technicians. However, ZAMBART has found success in conducting intensive training courses for Grade 12 school leavers to equip them to serve as laboratory technicians and smear microscopists and this method could potentially work in other resource-limited environments.

ZAMBART-trained microscopists working in Lusaka's bustling urban Kanyama Clinic. The clinic sees roughly 10,000 TB suspects per year.

Using technology to improve TB diagnostics in Zambia

Over the past several years, ZAMBART has sought to bring the utilization of existing Western technologies to the forefront of the fight to stop TB in Zambia. Through the procurement and subsequent field testing of TB diagnostic equipment and hardware, ZAMBART strives to strengthen existing TB control systems in the country, streamline and improve the patient-provider interaction and allow for more accurate and timely specimen analysis. ZAMBART has linked with the Foundation for Innovative New Diagnostics (FIND) to field test liquid TB culture systems[ii], rapid TB identification tests and Interferon Gamma Release assays (IGRAs) for TB infection[iii].

In resource-limited settings like Zambia, the principal diagnostic tool for identifying TB is sputum smear microscopy, which is known to have low sensitivity, especially when used in areas with high burden of human immunodeficiency virus (HIV) infection. In areas of high dual TB and HIV infection, mycobacterial culture is a more sensitive and specific means of diagnosing TB. While liquid culture is the gold standard for the diagnosis of TB in high-income countries, resource-limited settings are dependent on conventional solid media as it can be prepared locally.

Recently, due to an increased need for more sensitive and faster culture methods, resource-limited settings have been encouraged to use the more expensive commercial liquid culture system such as Mycobacteria Growth Indicator Tube (MGIT). ZAMBART conducted a feasibility study of the MGIT (August 2006 - August 2007) to test TB specimens in both liquid culture alongside solid culture[iv].

Encouragingly, the MGIT system has proved to be a rapid, easy-to-use technique with a high sensitivity for detection of mycobacteria directly from clinical specimens. Historically, large scale MGIT evaluation studies have not been performed in resource-limited settings. However, ZAMBART was able to conduct a four-way comparison of MGIT 960, manual MGIT and two types of Lowenstein-Jensen (LJ) culture media on routine specimens received in a national reference laboratory in a resource-limited setting. The results of this evaluation formed the major part of the report presented to the World Health Organization Stop TB Advisory Group (STAG) which resulted in a new recommendation for the use of liquid Tb culture in resource-limited settings.

Digital chest x-ray

ZAMBART has also partnered with Delft Diagnostic Systems, the Lung Institute University of Cape Town and the Image Science Institute University of Utrecht in a project seeking to develop a computer aided diagnostic (CAD) tool for reading chest x-rays to help diagnose tuberculosis in areas where there is no radiologist. The study is underway (2009 - 2010) and ZAMBART is testing out the use of an Odelca-DR containerised digital chest x-ray facility in a busy Lusaka clinic and providing images to be used to develop the CAD.

The digital chest x-ray machine is in a 20-foot container box, which weighs 5 tons and also holds a computer and its own energy supply. With the digital chest x-ray machine in place, those with very little training can easily take the images and once taken they are immediately stored in a database which can be accessed by clinicians. The images in this database are being used to develop a computer aided diagnostic (CAD) for diagnosing TB so that x-rays can be interpreted where there is no trained radiologist.

The unit was officially opened by the Zambian Minister of Health, Honourable Kapembwa Simbao and the Royal Dutch Embassy in Zambia's Health & HIV/AIDS First Secretary Mr. Peter de Haan on August 16, 2009 in Lusaka.

The new Odelca-DR digital chest x-ray machine was supplied by Dutch firm Delft Imaging Systems.

ZamLab CTL

Another new TB diagnostic facility currently in use in Zambia is the ZAMBART containerised laboratory (ZamLab CTL). Rapid delivery of sputum specimens to a central laboratory is difficult in Zambia, due to the great distances and poor roads. To combat this problem, ZAMBART worked with stakeholders, including the Zambian Ministry of Health (MoH), to develop a decentralized approach toward laboratory analysis by placing four containerized BSL3 laboratories, each capable of processing 100 sputum specimens per day in strategic locations. Four containerised laboratories have been placed at MoH facilities in Lusaka, Kabwe, Ndola and Livingstone as part of a comprehensive TB prevalence survey undertaken by ZAMBART in the country.

The key to the design of the ZamLab CTL was making maximum use of a very limited space in order to create a small, but highly-efficient BSL3 laboratory. The robust nature of a containerised laboratory ensures not only the integrity of the specimens and cultures, but also the maintenance of a comfortable and safe environment for the biomedical scientists and technologists working inside. In addition, each lab is equipped with air-conditioning and a power generator and is divided into three sections: specimen receiving, vestibule, specimen processing and culture.

Containerised laboratories may be a useful tool for performing large-scale TB prevalence surveys in areas with underdeveloped transportation networks. In addition, this design may serve as a model for expanding and decentralising TB diagnostic capacity in many parts of the world[v].

The Zambian Ministry of Health Permanent Secretary, Dr. Velepi Mtonga was on hand to officially open the ZamLab CTL in Lusaka on October 7, 2009. The event was also covered by the local and national media.

ZamLab CTL: Interior, exterior front and exterior rear view.

i World Health Organization. Global TB report. Global tuberculosis control: surveillance, planning, financing. WHO report 2007. WHO/HTM/TB/2007.376. Geneva, Switzerland: WHO, 2007.

ii Shanaube K, De Haas P, Schaap A, Moyo M, Kosloff B, Devendra A, Raby E, Godfrey- Faussett P, Ayles H. Intra-assay reliability and robustness of QuantiFERON-TB Gold In-Tube test in Zambia. Int J Tuberc Lung Dis, February 2010 The Union.

iii Raby E, Moyo M, Devendra A, Banda J, De Haas P, Ayles H, Godfrey-Faussett P. The Effects of HIV on the Sensitivity of a Whole Blood IFN-γ Release Assay in Zambian Adults with Active Tuberculosis. PLoS ONE. June 2008.

iv Muyoyeta M, Schaap J.A., De Haas P, Mwansa W, Muvwimi M.W., Godfrey-Faussett P, Ayles H. Comparison of four culture systems Mycobacterium tuberculosis in the Zambian National Reference Laboratory. Int J Tuberc Lung Dis 13(4):460-465, 2009 The Union.

v Kosloff B, de Haas P, Ayles H. Use of Containerized Laboratories in the ZAMSTAR TB Prevalence Survey in Zambia. ZAMBART Project, Lusaka, Zambia and London School of Hygiene and Tropical Medicine, London, UK. Presented at the 40th IUATLD Conference, Cancun, Mexico, December 2009.

IMPLICATIONS FOR POLICY AND PRACTICE

- **Measure the impact of new technologies:** It is important that new and innovative research be carried out to measure the impact of new diagnostic tools, keeping in the mind the impact of these tools not only on patients but on the larger health and TB control system in place within the country. It is also important to evaluate whether or not new diagnostic tools actually reduce mortality, an often overlooked indicator of measurement that should be addressed.
- **Assess the feasibility of new tools:** It is critical to analyse the feasibility of new diagnostic technologies, taking into account the external factors (human resources, financial costs and environmental impact) in implementing new tools for impact on a larger scale. Financial and environmental implications could also have a strong bearing on whether or not these technologies are actually taken up by local administrators on the ground.
- **The relevance of local research to global policy:** Research conducted in the developing world has significant implications for TB control policies globally, as evidenced by the research ZAMBART conducted on liquid culture tests, which was adopted by the World Health Organization and helped to create the policy on liquid culture testing worldwide. The application and measurement of emerging TB diagnostic technologies in the developing world will play a key role in the breakthrough required to halt the epidemic. Questions remain about how best to demonstrate the impact that these technologies have beyond the laboratory. Appropriate study designs to assess impact on health systems and health outcomes such as mortality are urgently needed if new diagnostic tools are to change lives in resource-limited settings.

About ZAMBART and TARGETS

The Zambia AIDS Related Tuberculosis (ZAMBART) Project is a Zambian NGO. ZAMBART was formed in 2004 through a collaboration between the University of Zambia's School of Medicine and the London School of Hygiene and Tropical Medicine (LSHTM), which spans more than 20 years. From the initial studies of the impact of HIV on the clinical presentation and outcome of tuberculosis, the scope of the research and the partnerships involved have expanded widely. Based in Lusaka, ZAMBART now collaborates closely with government, non-governmental and academic institutions within Zambia, Africa and the rest of the world. ZAMBART staff form an interdisciplinary team with a range of expertise including epidemiology, clinical science, social science, laboratory, operations research, health systems and services research, health policy analysis, health economics, development communication and counselling.

ZAMBART focuses on the overlap between HIV and TB in order to improve the quality of life of people affected by the dualepidemic. Conducting research within a limited resource setting, ZAMBART is committed to:

- Bridging research and action through operational research and through forging effective collaboration with local stakeholders;
- Providing evidence-based and high quality research;
- Addressing relevant and priority questions;
- Capacity building for Zambian research - scientific and managerial

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ZAMBART is a core member of The Team for Applied Research Generating Effective Tools and Strategies for Communicable Disease Control (TARGETS) led by LSHTM. TARGETS is a Research Programme Consortium funded by the UK Department for International Development (DFID). The Consortium brings together partners in Sub-Saharan Africa, India and Europe working towards better health for the poor and vulnerable through more effective communicable disease control.

www.targetsconsortium.org

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