

PROJECT SUMMARY OF MODS LAB AT IHK JULY 2007

With money raised by Suubi Trust and Dr Mark Russell, International Medical Foundation is in the process of developing a level 3 bio-containment facility at International Hospital Kampala to provide a MODS TB culture and sensitivity service. This facility will be used to:

- 1. Provide TB culture and sensitivity testing at cost price – currently estimated at \$5 per test**
- 2. Train Ugandan technical staff to work in, manage and set up TB diagnostic centres**
- 3. Establish a consultancy program to promote best practice in TB diagnostic services at District level throughout East Africa**

Program Goals

- To facilitate the adoption of a low cost TB culture and sensitivity testing technique in East Africa (at \$5 per test)
- To make TB culture and sensitivity testing mandatory investigations in the management of patients who may have TB even in a low resource setting
- To increase the proportion of patients with TB in Uganda who are successfully diagnosed and treated
- To recognise and act on the increasing problem of drug resistant TB

Program Objectives:

- To establish a level 3 bio-containment facility for TB diagnostics at International Hospital Kampala
- To offer rapid, **low cost** and high sensitivity TB culture and sensitivity (MODS) to the Private, Public and Private Not for Profit health sectors
- To offer a high quality TB culture and sensitivity service at a cost price of \$5 so that the price is affordable and the service is self financing
- To provide training in the use of the MODS test
- To provide a consultancy service to promote best practice in TB diagnostic services in East Africa

PROJECT SUMMARY OF MODS LAB AT IHK JULY 2007

Why concentrate on TB and MDR TB?

Every year, 1.7 million people globally die of tuberculosis, which has been for many years a curable disease. The poor are disproportionately affected, and tuberculosis further impoverishes individual people and societies and because in many countries tuberculosis is a curable and preventable, in large parts of the world it had stopped being viewed as a priority. However, the development of a strain of TB that does not respond to medication is causing major global concern. Multi Drug Resistant TB (MDR-TB) has a much higher mortality and is much more expensive to treat, and it is becoming increasingly common as misuse of antibiotics has allowed resistance to the treatments that used to work well to grow.

While drug susceptible TB can be cured by antibiotics within six to eight months, MDR-TB requires much more powerful and expensive drugs that need to be taken for more than two years, and often with adverse side effects. Yet only 50 percent of patients who contract MDR-TB get cured. MDR-TB is also much more difficult and more expensive to treat than drug susceptible TB. A single patient can require between \$10,000 - 20,000 as evidenced by cases being handled by the aid agency MSF in Kenya.

As a result of this, Goal 6 of the Millennium Development Goals (MDGs) of the United Nations includes the halting and reversal of the rising incidence of tuberculosis, and the Stop TB Partnership aims to halve the prevalence of tuberculosis and resulting deaths by 2015.

Uganda records an estimated 80,000 new cases of tuberculosis every year. Of these, it is estimated that half are among people who are also infected with the HIV virus that causes AIDS. Among this population, it is more difficult to get a diagnosis using microscopy (which is the test that is most widely available). The disease affects mostly people in the 15-49 age group and often kills within two years if not treated, according to the health ministry. Recent research suggests that around 12% of new cases of TB in Uganda are resistant to some drugs.

Of the estimated 80,000 new cases of tuberculosis (TB) in Uganda every year¹, only 49% are detected.² Early detection of MRD TB is extremely important, and it is the cornerstone of the global TB strategy. Therefore, developing the capacity of laboratory services is an essential step towards improving the health of the Ugandan people. It both improves the patient's chance of being fully treated and to limit the amount of time that they are potentially infecting others, which is why getting a prompt and accurate diagnosis quickly is crucial. An accurate diagnosis in this case means one where we not only establish that the person is sick with TB, but what drugs that TB will respond to. This is called sensitivity testing.

What is testing for sensitivity?

There are several ways to establish a TB diagnosis in patients. Commonly, doctors will start treatment on the basis of the symptoms that the patients describe and that they observe. Normally they will also send a sample to the lab for microscopy, because sometimes the bacilli that cause TB can be seen under the microscope. Currently, positive diagnosis of TB in Uganda depends on sputum smear microscopy. However, even when performed well the sensitivity of this technique is 40-60% and possibly as low as 35% in patients with HIV infection.

¹ UNOCHA – Integrated Regional Network release 28.03.07

² <http://www.reliefweb.int/rw/rwb.nsf/db900sid/KHII-7285C3?OpenDocument>

PROJECT SUMMARY OF MODS LAB AT IHK JULY 2007

They can also send the sample to be cultured. That means that the sample is grown. TB culture remains the gold standard diagnostic test with a sensitivity of over 90%. The National TB Reference Laboratory in Uganda currently uses the Lowenstein Jensen solid culture medium technique. This takes 3- 8 weeks to yield a positive result, with drug sensitivity taking even longer. Sensitivity means that once the TB is being grown there is an opportunity to find out some more about the strain that the person has. Different drugs can be tried out on the mycobacterium and it can be seen which ones kill them, or what they are sensitive to. This means that, after this test, we can be certain that the treatment we give will cure the patient.

The problem is therefore that, as described above, culturing TB and getting sensitivity information has been either very slow (taking up to three months) or expensive (requiring very modern technology).

How will MODS help?

MODS represents an important step forward in achieving routine culture and sensitivity testing for all patients suspected of having TB. The method has been developed by a research team based in Peru, where it has demonstrated high levels of accuracy faster, and at a fraction of the price of other sensitivity tests. The technology required to start using the techniques is minimal, and the cost of the reagents and equipment low, which means it is a great test to use in resource poor settings.

The following extract is from a New England Journal of Medicine article published in October 2006 ([*Moore et al – N Engl J Med 2006 – 355; 15: 1539-50*](#)):

“ The microscopic-observation drug-susceptibility (MODS) assay for the detection of tuberculosis and multidrug-resistant tuberculosis, directly from sputum, relies on three principles: first, that *Mycobacterium tuberculosis* grows faster in liquid medium than in solid medium; second, that characteristic cord formation can be visualized microscopically in liquid medium at an early stage; and third, that the incorporation of drugs permits rapid and direct drug-susceptibility testing concomitantly with the detection of bacterial growth.”

The WHO supports the introduction of liquid broth culture techniques for more rapid TB diagnosis. These techniques are usually semi-automated using expensive machines. The MGIT technique is available in Kampala for \$65 per culture and sensitivity test and takes 10-16 days for a positive result. MODS is a much simpler, quicker, manual, liquid broth technique that relies on basic laboratory equipment. MODS is currently the cheapest and fastest of the new generation of liquid broth techniques.

The evidence that MODS works as well as these more expensive methods is very good. In the Peru study ([*Moore et al – N Engl J Med 2006 – 355; 15: 1539-50*](#)), 3760 sputum samples were taken from patients judged clinically at risk of having TB. 401 (10.7%) yielded cultures positive for *Mycobacterium tuberculosis*. Sensitivity of detection was 97.8% for MODS culture, 89.0% for automated mycobacterial culture, and 84.0% for Löwenstein–Jensen culture (P<0.001); the median time to culture positivity was 7 days, 13 days, and 26 days, respectively (P<0.001), and the median time to the results of susceptibility tests was 7 days, 22 days, and 68 days, respectively.

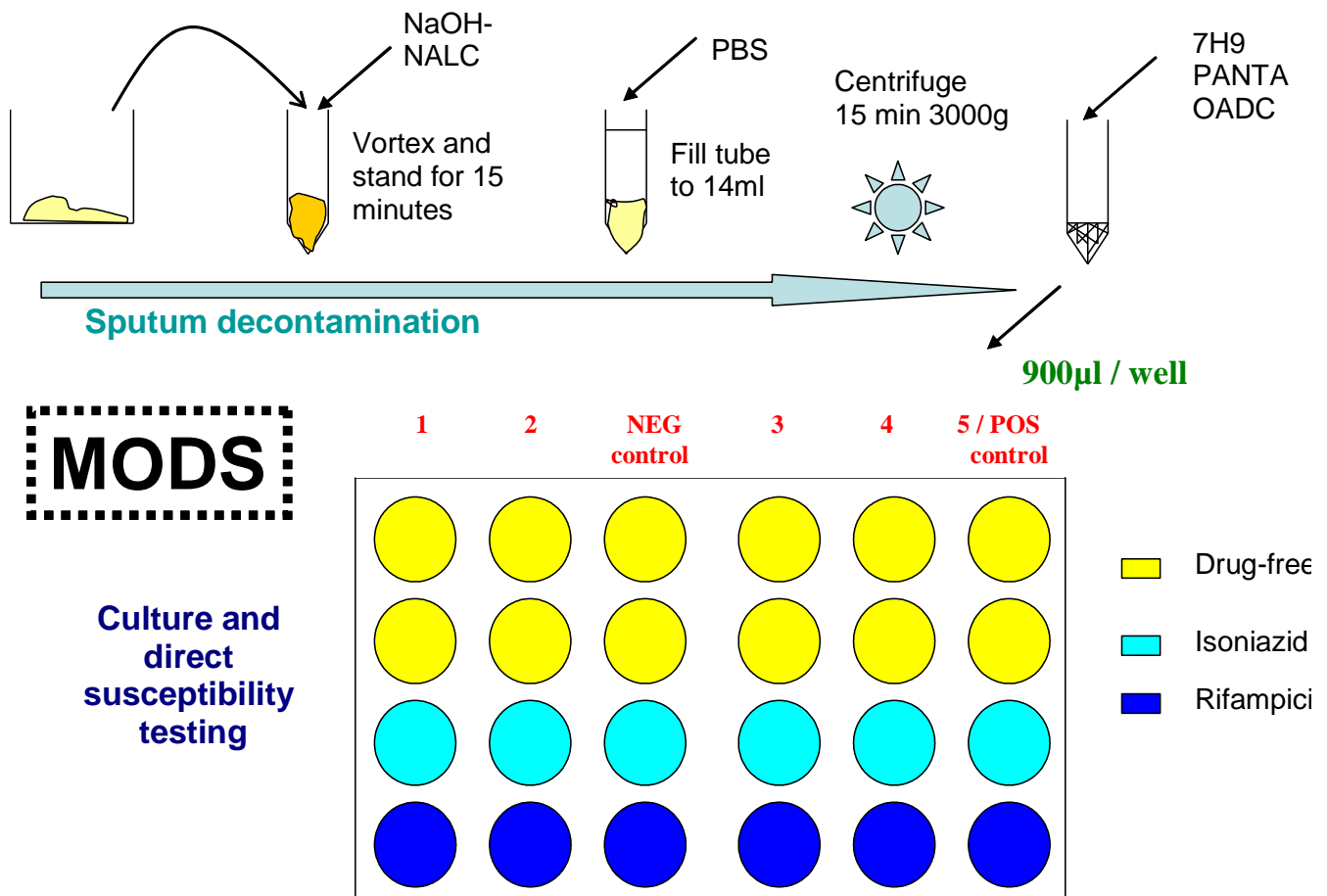
**PROJECT SUMMARY OF MODS LAB AT IHK
JULY 2007**

The MODS technique

To perform a test (start a culture), a sputum sample is treated to decontaminate it for other micro-organisms and then concentrated by centrifugation. Enriched liquid medium (to enhance the growth of the Mycobacterium) is placed into a series of wells in a tissue culture plate. Two wells are further treated with rifampicin and isoniazid to identify MTB that is resistant to these antibiotics. All four wells are inoculated with the treated and concentrated sputum specimen. From day 5 the tissue culture plates are examined every day under an inverted light microscope. The distinctive cord-like shapes of MTB become visible at between 7 and 10 days.

The technique is described in detail in the **MODS USERS GUIDE** at:

<http://www.upch.edu.pe/facien/dbmbqf/mods/MODS%20user%20guide.doc>



**PROJECT SUMMARY OF MODS LAB AT IHK
JULY 2007**

MODS Project : 5-Year Plan

	FY.1	FY.2	FY.3	FY.4	FY.5
Laboratory staff recruited and equipment and reagents purchased					
MODS technique rolled out to at least one major partner organisation (Reach Out Mbuya).					
Lab services are quality controlled and audited					
Marketing material has been produced and distributed					
Model contracts are established for purchaser organisations					
Guidelines published to promote MODS for the diagnosis of TB within current WHO and Ugandan guidelines					
Guidelines distributed to promote MODS for the diagnosis of TB within current WHO and Ugandan guidelines					
Lab is processing 100 sputum cultures per week					
Lab has trained 2 technicians in the use of MODS					
MODS technique adopted by at least one other laboratory					
Lab is processing 200 sputum cultures per week					
Lab is training a minimum of 4 technicians per year in the use of MODS and advising on low cost options for establishing the service in district laboratories					
MODS technique adopted by a further 2 laboratories					
MODS technique adopted by a further 4 laboratories					

THE VALIDATION PROCESS

MODS has been validated as an effective TB culture technique with a sensitivity of 97.3% and specificity of 99.7% ([Moore et al – N Engl J Med 2006 – 355; 15: 1539-50](#)).

With this level of accuracy noted elsewhere the evidence base for the test is very good. However, it is also important to demonstrate that when we do the test, in Uganda, that the results are also so good. The validation we want to do is to further confirm its efficiency in a different context. Therefore we need to double test the first three hundred samples with another method to make sure we get the same result.

The plan is therefore as follows.

We will also perform a validation exercise on first roll out of MODS in Uganda:

- Our first 100 MODS culture tests will be crosschecked on L-J medium.
- Our second 100 MODS culture tests will be crosschecked by MGIT.
- On completion of the validation exercise we will publish a report in the form of a letter to a reputable medical journal describing our results.