



New Screening Solution Offers Hope in the Battle Against TB

info@rapidbiosensor.com Tel +44 (0)1223 264 558 © 2008 Rapid Biosensor Systems

Dennis Camilleri, CEO, Rapid Biosensor Systems

dennis.camilleri@rapidbiosensor.com

Tel: +44 (0)1480 390648

In recent years, a number of 'old' diseases have re-emerged as significant threats to world health, driven by factors such as population migration and modern transportation. Of particular concern is the increase in the incidence of tuberculosis (TB) infection, a highly contagious disease spread through the air when infected people cough, sneeze or spit. According to statistics published by World Health Organization (WHO), 8.8 million active cases of TB are diagnosed each year – 25,000 every day – and of these patients, almost 2 million die – approximately 5,000 every day. Although most cases occur in the world's poorest countries, no region is free from the threat – infection levels are rising in Western Europe, for example.

Improved diagnosis is central to efforts to halt the spread of TB. While developing new and better medicines are important, effective diagnosis provides health workers with essential information about the source of the TB and enables them to implement the right treatment, avoiding wasting both time and valuable resources. An obstacle to effective diagnosis, however, is the notable absence of a fast, reliable and cost-effective method of diagnosis. Most countries still rely on a technique developed over 100 years ago – microscopy examination of sputum – which, WHO estimates, achieves only 40-60% test sensitivity under field conditions, a figure that can fall to 20% in patients who are co-infected with HIV.

A vital first step towards improved diagnostics is rapid and accurate screening at the point of care, but here too the existing solution – the Mantoux TB skin test - is not up to the challenge. The test involves a health worker injecting testing fluid (tuberculin) under the skin of the patient's arm, then waiting between 48 and 72 hours to see if there is a reaction – a red swelling on the injection site - indicating the presence of TB. The diameter of the swelling shows if the patient has been exposed to TB, but factors such as the patient's health and age have to be taken into account. This requirement for expert assessment also introduces a degree of subjective interpretation to the test. Final results of the test can take as long as two weeks.

A further disadvantage is the tendency for the test to produce both false positive and false negative results. False positives may occur in patients who have been immunised against TB with the BCG vaccine or had a previous infection that has been cleared up. The test can return a false negative if patients are suffering from a variety of other illnesses or are taking certain medications that lower their immunity.

In the light of these issues, WHO's strategy for controlling TB includes developing faster screening solutions that identify patients with active TB with a higher degree of accuracy than the Mantoux test. Furthermore, given that TB is most prevalent in the poorest countries, it should ideally be low-cost and capable of administration by personnel with minimal training. Researchers are currently exploring the potential of a variety of technologies, including several based on detecting the release of Gamma Interferon in response to mycobacterium. However, at the time of writing the most promising results have been produced using bio-optical sensor technologies developed by Rapid Biosensor Systems (RBS), a UK-based technology development company with extensive experience in medical diagnosis, optics, biochemistry and industrial design. After six years' research and development, the company's TB Breathalyser is currently undergoing final pre-production testing at selected sites around the world.

The RBS TB Breathalyser is a non-invasive screening solution that is portable and produces almost instant results. It can be assembled without the need for clean room conditions and may be used by non-medical personnel, making it particularly suitable for use in developing countries.

How it works

The TB Breathalyser comprises a single-use disposable sample collection tube and a multi-use reader. The patient coughs into the collection tube, at the bottom of which is a glass bio-sensor coated with a patented bio-chemical coating formulated to react with the TB bacilli. A simple push-and-twist action automatically seals the sample in the tube and deposits it on the bio-sensor. The tube is then inserted into the reader and twisted to switch on the unit.

The TB Breathalyser analyses the sample by performing a displacement assay employing evanescent wave technology, an established biochemical process that is proven and fast. A diode laser in the reader interrogates the bio-chemical coating, which contains analogues that are coated with a fluorescent material. In the displacement assay process, the TB antigen displaces fluorescently-coated analogues and bonds more strongly to antibodies, causing a reduction in the fluorescent signal after excitation by the laser. The laser detects this signal change and the unit returns a positive result. Reading and analysis of the sample takes approximately two minutes, and from start to finish, the entire screening process takes just a few minutes. After use, the sample tube is destroyed.

The TB Breathalyser has very high specificity and sensitivity, the former in the order of 100% and the latter in excess of 95% (the WHO's guidelines for TB screening are 60% and up to 95% respectively). Unlike the Mantoux test, the TB Breathalyser is not compromised by the presence of other infective agents, so other respiratory tract conditions are discounted and only early stage TB and actively infectious TB will be recognised. Furthermore, the presence of HIV as a masking agent is ignored – an important consideration in the light of the co-existence of TB and HIV in the populations of many developing countries. RBS's state-of-the-art bio-optical technology is protected by comprehensive and robust international patents.

Successful clinical trials

The performance of the RBS TB Breathalyser has been validated in a series of clinical trials with over 500 patients within a hospital environment. In addition, the system has successfully passed completely independent trials in Ethiopia under the supervision of the London School of Hygiene and Tropical Medicine and at a WHO-approved TB hospital in India. A trial is also currently in progress at a further WHO-approved hospital in South Africa, results of which are expected in December 2008.

Dr Ruth McNerney is a senior lecturer at the London School of Hygiene and Tropical Medicine, Britain's national school of public health and an internationally-recognised centre of excellence in tropical medicine research. She has been closely involved in the Ethiopian trials and comments as follows on the potential of the TB Breathalyser:

“Although we have effective drugs against tuberculosis, it remains one of the world's most serious public health problems and kills more adults than any other single infectious agent. We urgently need ways of detecting infectious pulmonary cases early in the infection before the disease has a chance to spread.

“Current tests are slow, clumsy, require specialist laboratory facilities and are only effective for detecting advanced disease. The RBS Breathalyser test is unique in that it does not require the collection of sputum samples, which are characteristic of advanced disease. That it does not need facilities such as electricity or running water and can be used outside of the hospital clinic means it could be used to screen people without them needing to visit the health centre.

“The RBS TB Breathalyser test is an exciting new development in TB control. It will help us learn more about when patients become infectious and how long they remain a risk to other people. In a small study in Ethiopia we used a prototype of the test to identify TB patients within ten minutes. It is important that further studies are undertaken to ascertain the sensitivity and specificity of the test. If the TB Breathalyser proves sufficiently sensitive then it might have a major impact on the way we control tuberculosis.”

In February 2005, RBS concluded a manufacturing and sales agreement with leading medical device supplier Clement Clarke International (CCI). Under the agreement, CCI will exclusively manufacture and distribute the TB Breathalyser for use in human TB screening applications. Starting in Q4 of 2008, CCI embarked on a programme of pre-production testing of the RBS TB Breathalyser in selected sites around the world. If the tests are successful, the Breathalyser is expected to be commercially available in the first half of 2009.



Future Applications

The partnership with CCI allows RBS to retain all its intellectual property rights and to collaborate with other organisations on new applications for the biosensor technology. The company has made considerable progress in adapting the technology to analyse liquid as well as aerosol samples, which will significantly broaden the potential applications for the solution. In particular, RBS has identified new market opportunities: sputum-based TB diagnostic testing, testing for bovine TB, testing for E. Coli in food and testing for malaria.

Sputum-based TB diagnosis: RBS is applying its patented technology to provide a rapid, laboratory-based test to replace the sputum smear and culture test. RBS's established USPs – ease of use, rapid availability of results, and low cost – will differentiate the RBS TB sputum test from current methods. At the time of writing, RBS proof-of-principle designs indicate that it will be possible to detect TB in sputum taken from actively infectious people, especially those in the early stages. The results would be available in minutes.

Rapid testing for bovine TB: Bovine tuberculosis (BTB) is highly contagious, reducing yields, especially of milk. Besides cattle, the disease is also found in other species, particularly deer and badgers. It was thought to have been largely eradicated in the UK by the 1970s, but it returned in the early 1980s and is now established in the Midlands, southwest and Wales. Around 2,000 cases are confirmed each year. RBS has completed proof-of-principle design for fluid/blood collector hardware and will shortly begin testing on animals.

Testing for E. Coli: The Centers for Disease Control (CDC) estimates that 73,000 cases of E. Coli 0157:H7 occur every year in the USA alone, with 2,100 patients being hospitalised and 61 dying as a direct result of E. Coli infection.

Testing for malaria: According to the US National Institute of Allergy and Infectious Diseases, some 2.24 billion people - more than 41% of the world's population - are at risk of acquiring malaria, and up to 3 million people will die each year from the disease. Approximately 2,000 cases occur every year in travellers returning to the UK from malaria-endemic countries. RBS's technology development programme will establish its ability to differentiate its products from competitors by offering competitive pricing for more accurate and rapid tests.

For further information please contact:

Rapid Biosensor Systems Ltd Babraham Hall, Babraham, Cambridge, CB2 4AT

Tel: +44 (0)1223 264 558

Fax: +44 (0)1223 265 684

Email: Info@rapidbiosensor.com