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Tuberculosis: well known for centuries – still difficult to diagnose

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TB (*Mycobacterium tuberculosis*) disease has been known by various names for thousands of years including consumption, phthisis, scrofula, Pott's disease, and the White Plague, and has of late been described in exquisite biological detail. Yet we still struggle to reliably answer the question: Does a particular person have 'active' TB?

In most of the world, until recently, TB has remained stubbornly persistent ('endemic'). A combination of improved living conditions and (largely) effective treatment has pushed TB into the margins of developed countries, but in much of the world, including Africa and Asia in particular, it remains a major epidemic causing of loss of productive, healthy and happy life. In South Africa TB is the leading cause of death although only 1% of the population develop TB disease every year. Globally US$ 0.7 billion is spent annually on TB research. It is calculated that annually approximately UDS$ 2 billion is required to develop new tests and drugs needed to eliminate the if the TB epidemic. Many fine details of the lifecycle of the 'infectious agent' (the TB bacillus) are known from the extensive research conducted. In contrast, the available diagnostic tests have several limitations and perform poorly especially in developing countries where they are most needed. The unsatisfactory performance and availability of diagnostic tests has consequences for clinical management, costs, surveillance, and systems planning of any TB program.

The course of TB disease makes an early diagnosis difficult.

The course of TB in the human is complex due to the slow multiplication of the TB bacterium. TB is spread by inhaling micro-droplets which contain the TB bacterium. These micro-droplets are generated during coughing bouts, especially by adults who have active pulmonary (lung) TB. The microdroplets are inhaled and settle in the lung where they slowly multiply. At this stage the person is said to be infected with TB (TB infection) but has not yet developed TB disease. It is particularly difficult to diagnose TB infection due to the small number of TB bacteria the person is infected with, as well as the poor performance of the available tests (skin reaction and blood-based tests) used to diagnose TB infection. Only a small proportion (<10%) of people infected with TB will develop TB disease in their lifetime (active TB). TB of the lungs (pulmonary TB) is the most common form of TB occurring in approximately 80% of cases and those with a compromised immune systemt, wo mazy be HIV-infected, diabetics, receiving cancer drugs or infants, are especially prone to develop TB disease. As the TB disease progresses, the person will start developing symptoms. Initially the person will cough up only a small number of TB bacteria making early TB disease particularly difficult to diagnose. On average, the time the TB diseases flares up (reactivates) to the time a diagnosis of TB disease is made can be about 6 weeks even when modern diagnostic test are used.

Over time, as the TB disease progresses in the lungs, the number of TB bacteria coughed up in the sputum (lung phlegm) increases exponentially. In a person with advanced disease it is estimated that up to 10^{10} TB bacteria per ml of sputum are coughed up making such a person highly infectious. During this phase the diagnosis of TB is easier to confirm.

The TB bacteria can then spread from the lungs through the body and this 'disseminated' TB disease can develop in any organs. TB in organs outside the lung, extra-pulmmonary TB, is particularly difficult to diagnose as the sputum of the infected person may no longer contain TB bacteria.

The limitations of the old TB tests

Some of the most commonly used and familiar diagnostic tests using chest X-rays and or growing the bacterium in culture, are more than 100 years old. Although changes seen on a chest X-ray might suggest TB disease, these changes do not prove that the patient has TB disease or give an indication if the TB bacteria are resistant to the commonly used anti-TB antibiotics. Although the culture of TB bacteria from the sputum of a person with TB disease is an accurate diagnostic test, it also has a numerous weaknesses. TB culture is expensive and

can take up to 6 weeks before it is known to be positive but once the bacteria have been grown in culture it can then be tested for resistance top various drugs. This is not acceptable as the disease will advance during the delay and the person will continue spreading TB in their household and community. In patients with severe suppression of their immunity, including people infected with HIV-infected persons the TB disease may spread so rapidly that the patient may die while waiting for their test result. The low sensitivity of chest X-rays and TB culture tests leads to the need to treat 'presumptively'. Presumptive TB is diagnosed when on assessing the signs and symptoms of TB, night sweats, sudden weight loss, persistant coughing or blood in the sputum, the doctor feels that the diagnosis of TB disease is highly likely even though there is no definitive proof that the patient has TB disease. The diagnosis is based on a risk benefit analysis when the risks of harm from the unnecessary use of the TB drugs are outweighed by the risk of not treating actual TB disease. The problem with this approach is that a high proportion of patients are unnecessarily treated for TB; estimated to be between 20% to 40% and this is no small matter as the anti-TB drugs have to be taken for 6 months with have numerous unpleasant side effects.

Even with Xpert we are not there yet!

It is evident that new diagnostic tests are required that can rapidly, within minutes or hours, diagnose TB disease. The test should be widely available, preferably in the clinic, be accurate and able to determine the TB bacteria's sensitivity to the available anti-TB antibiotics. The tests most likely to meet these requirements are based on the molecular analysis of the TB bacterium genes. The most promising of the new tests is geneXpert MTB/RIF often referred to as just Xpert. This is a molecular test, using modern DNA technology to detect the presence of TB bacterium in the sputum. The system is easy to use and can be performed in a basic laboratory. Xpert has a detection sensitivity that is similar to the six week TB culture methods but has one major advantage – namely that the results are available within 2 hours of starting the test. In addition the Xpert also gives the physician an indication whether the TB bacteria are sensitive or resistant to the commonly used anti-TB antibiotics preventing patients with resistant TB being started on incorrect treatment. The limitations of Xpert are that it is expensive, costing about US$ 100 per test, needs a small laboratory with a constant electrical supply and may not diagnose extra-pulmonary TB. For these reasons Xpertd is still not available in every clinic and ways need to be found to make this technology more widely available. Xpert is of limited value in children and patients with advanced HIV as they cough up a small number of TB bacteria below Xpert's detection threshold but new machines, Xpert Ultra, with a lower detection threshold have been developed and are being field tested at present.

What would be the ideal TB diagnostic test?

Although Xpert has resulted in improved diagnosis of TB disease it is still far from the ideal diagnostic test. To make a difference we need diagnostic tests, available in all clinics, that are simple to perform on samples that are easy to collect from all patients including infants and children. Tests that depend on difficult to obtain samples will be of limited value. Babies and young children cannot cough up phlegm that is easily collected. At present stomach washings (gastric aspirates) or samples by sucking the phlegm from the back of the throat (induced sputum) are commonly collected to diagnose TB disease in children. However, these tests are invasive and unpleasant for both the child and the nurse performing the test. For this reason new tests must be able to analyse easy-to-collect samples sucxh as saliva, stools, urine or a drop of blood.

Tests to distinguish between TB infection and TB disease

A test that could differentiate between TB infection and TB disease would be of great value. If it were possible to accurately diagnose people infected with TB, we would be able to cure people more quickly and limit transmission to others. Recent studies have shown that TB infection can be successfully treated with 12 doses of antibiotics, taken weekly, with minimal side effects. This would be a major step forward in eliminating TB. Another approach would be a vaccine which could prevent a person from developing either TB infection and/or disease. Unluckily after numerous attempts it is estimated that an effective vaccine will not be freely available in the next 20 years.

Tests to predict the response to therapy

The flipside of diagnostics, using much the same biological and engineering ideas, is monitoring of

'treatment response' by quantitatively checking the progress of treatment. It is increasingly clear that not all patients being treated for TB require a 6 month course of treatment and tests that predict the patient's response to therapy would be of great value. Patients with a favourable response could be treated with a shortened course while those with a poor response would require prolonged therapy. This would prevent patients not only from taking unnecessary therapy but also reduced the risk of developing unwanted side effects from the treatment.

The goal of the World Health Organization is to eliminate TB by 2050. To be able to achieve this goal we need new point of care diagnostic tests, to be able to accurately distinguish between TB infection and TB disease and have tests which accurately predict cure. We do not only need new diagnostics but also new and more powerful anti-TB antibiotics.

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